THIRD EDITION

PRINCIPLES OF CRITICAL CARE

Farokh Erach Udwadia

JAYPEE

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OF
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Principles of Critical Care

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Dedicated to

Vera and my children, for the love and happiness we share; my parents,
for showing me the way; my house-staff and nursing staff,
for their unstinted support; my patients for teaching me all I know.

Preface to the Third Edition

It is gratifying that this book titled *Principles of Critical Care* continues to be the standard text for critical care in India, and that it is now also read in countries outside India. The Third Edition of this book has been overdue. The task has been onerous, difficult and very demanding, but is at last completed. I felt it would be unwise to attempt at being encyclopedic in both reach and content (as observed in many Western texts) and have therefore elaborated particularly on problems often and commonly observed in intensive care units in our country. It is indeed difficult to strike a balance on what to include, what to elaborate upon and emphasize, what to exclude and yet give a reasonably coherent account of the subject. I do hope this balance has been achieved.

Almost all the chapters have been revised and many of them have been extensively rewritten. These include the section on Cardiopulmonary Resuscitation and Cerebral Preservation in Adults, Clinical Shock Syndromes, Critical Care of the Transplant Patient, Nosocomial Infections, Neurological Problems, Organ System Dysfunction Requiring Critical Care, in particular, Acute Pancreatitis and Critical Care in Acute Hepatic Failure. Besides, a new chapter titled End of Life Care in the Intensive Care Unit has also been included in this book.

The present edition has an excellent format, far better than the earlier two editions. The quality of paper, the quality of illustrations, line drawings, algorithms, tables, boxes and, above all, the quality of numerous images that illustrate the text leave nothing to be desired.

I am very confident that this book will continue to be beneficial to intensivists, anesthesiologists, physicians, surgeons, colleagues practising other specialties, as also to trainees in critical care, to residents, students and nursing staff.

I very sincerely acknowledge my thanks to my distinguished contributors who have once again collaborated in an honorary capacity to this edition, thereby enhancing its prestige. I would like to express my deep gratitude to Dr Khyati Shah, my research assistant, without whose help this work would not have been possible and to Mr Neeraj Chavan for his dedication, unstinted help and support. I thank Dr Aruna Poojari for her suggestions and help with the chapter on Nosocomial Infections and Dr Shilpa Bhojraj for her assistance with the chapter on Control of Pain and Anxiety and the Use of Muscle Relaxants in the Critically Ill Patient. I am grateful to AV Graphic Designs Pvt Ltd (Mumbai) for creating excellent illustrations and tables and also to Jaypee Brothers Medical Publishers (P) Ltd for reproducing them. Their cooperation and punctuality during the course of this work has been outstanding. I thank the publishers and authors who have granted me permission to publish some figures from their books/journals. Although every effort has been made to trace copyright holders of material printed in the book, in some cases the copyright holders are yet to respond. The publishers will be glad to hear from them.

My gratitude above all to my wife, Mrs Vera Udwadia, for correcting page proofs and for her forbearance and care during the many days and nights spent on this work.

Finally, my sincere thanks to Mr Jitendar P Vij (Group Chairman), Mr Ankit Vij (Managing Director) and Mr Tarun Duneja (Director-Publishing) of M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India and Mumbai Branch for their support in publishing this book.

Farokh Erach Udwadia

Preface to the First Edition

Critical care in India and other developing countries is nascent and needs to strike deeper roots if it is to flourish and prosper. The history of critical care in this country started in the late sixties and early seventies with the establishment of coronary care units in Mumbai and in a few other big cities of India. These units, though centralized, were designed and equipped chiefly to offer intensive care to patients with acute myocardial infarction. They had a poor concept of overall critical care, or of intensive respiratory care. Mechanical ventilator support was primitive, its use being mostly restricted to a token gesture of grace offered to a patient about to depart from this world. In the mid and late sixties, my medical unit at the Breach Candy Hospital, Mumbai, started offering overall critical care, intensive respiratory care and successful ventilator support in critical illnesses due to a wide spectrum of disease. Intensive care in my unit, to start with, lacked good monitoring facilities and was initially offered in a few separate rooms within a general ward of the hospital. These were perhaps the first stirrings of critical care as we know it today in the city of Mumbai, and perhaps in this country. However, the real impetus to organized, centralized, overall critical care arose when, in early 1970, a 34-year-old, 6-month pregnant lady was hospitalized in my unit at the Breach Candy Hospital for increasing breathlessness. She was dubbed as functional by the duty officer, when, in fact, she had acute poliomyelitis presenting with intercostal muscle weakness. She evolved over 24 hours because of bulbar and spinal involvement into an acutely ill, totally paralytic state which needed intensive care of multiple organ systems, together with prolonged ventilator support. We used a pressure-cycled Bird's ventilator, and with the able assistance of an anesthetist colleague, Dr Bhatia, struggled and succeeded against great odds in keeping her alive. Successful ventilator support was continued for many months, and she was delivered by caesarean section of a healthy baby at full term, whilst on ventilator support. About 6 weeks after initiating ventilator support, we fortuitously acquired a Radiometer through the patient's brother who was a pediatric cardiac surgeon in Los Angeles, enabling us thereby for the first time to monitor arterial pH and blood gases by the Astrup technique. This was indeed the first blood gas analysis machine used for intensive patient care in this country. Unwittingly, the illness of this dear lady (who is still well) became an important landmark in the history of critical care both in this city and in this country. Starting in 1971, from a two-bedded, centralized, reasonably well-equipped, multidisciplinary all-purpose intensive care unit, we graduated to a newly constructed eight-bedded well-designed and fully equipped unit which admitted critical problems in all branches of medicine and surgery. This unit over many years continues to have a medical audit as good as any unit in the West. It has also served to train numerous house physicians and registrars who have carried the message of critical care to other hospitals of this city and to many hospitals in other parts of the country. The concept of critical care has now been increasingly accepted and followed in most large hospitals of the big cities of this country.

Some of my colleagues, particularly those engaged in community medicine, preventive and social medicine, are of the opinion that in a poor large country like India, the encouragement of critical care is a misdirected effort. It is indeed true that increasing the number of critical care units in the country will not inflict even a small dent in the overwhelming health problems this country has to cope with. Should then the speciality of critical care be fostered and encouraged? The answer on principle is unquestionably yes. It is the physician's duty to care for the ill, and the more critically ill a patient, the more intensive the care a patient needs for survival. We however need to do this in all poor countries with a logical perspective. It would be unrealistic, futile and morally wrong to dot this huge country with numerous critical care units when even basic primary health care is lacking, and when ordinary hospital facilities in most parts of the country are hopelessly inadequate. Reason demands that well-equipped critical care units should in the foreseeable future be confined to medium and large hospitals which have the infrastructure to support such units. It would also be wiser and profitable to organize general all-purpose intensive

care units rather than copy the West and establish critical care units in different specialities and subspecialities. A multidisciplinary intensive care unit permits concentration of meager resources with regard to staffing, equipment and technical expertise. Above all, it encourages a more holistic approach, so that problems in the critically ill are considered in an overall perspective rather than in terms of disease afflicting isolated organ systems. There is also a crying need to formulate laws and regulations (non-existent at the present time) that govern the establishment and functioning of critical care units in the developing countries. Financial lucre will otherwise continue to allow the mushrooming of so-called intensive care units which are veritable death traps for unwary, unsuspecting patients.

Efficiently functioning critical care units in the foreseeable future will be largely confined to the big cities of this country. Should we not promote a modicum of better care for critical illnesses in the huge population of over 650,000,000 that resides outside these cities? This can for the present only be achieved by providing a better staffed and better equipped high-dependency ward in every district hospital of this subcontinent. These wards would not qualify by Western standards as critical care units, but in our experience, could offer better care, with improved results, at a smaller cost.

This book is largely based on my numerous jottings and notes embodying my experience of problems in the diagnosis and management of critically ill patients over the last 30 years. A book of this magnitude, authored in the main by a single individual helped by just a few distinguished contributors, may seem audacious, but has the intrinsic advantage of presenting the uniform view of one who for many years has had to grapple with a wide spectrum of critical illnesses. It in no way detracts from the fact that for a successful outcome, critical care often needs team effort involving many specialities in medicine, surgery and their allied branches. The emphasis in this book is on fundamentals that form the basis of care and on important problems that find their way to a busy unit. The book also includes in most chapters an insight into the nature of derangement of altered functions in a critical illness. Good management can then be better understood and need not be ritualized or didactic.

Critical care in developing countries encompasses both diseases prevalent in the West, as also special problems chiefly encountered in poor countries such as India. These problems particularly in relation to important fulminant tropical infections have been given due emphasis in this book. We also have to necessarily contend with the lack of sophisticated gadgetry and equipment in many of our units. The successful management of many life-threatening problems under these circumstances and restraints is difficult but still possible, and has been discussed in relevant chapters.

It is essential to stress that the principles of good critical care are the principles of good medicine and surgery. Improvement in critical care can, therefore, only flow from improved standards in general medicine and surgery. A careful history, a good physical examination, and the evaluation of relevant laboratory and imaging data will always form the bedrock for correct diagnosis and management of life-threatening problems. Improved technology and invasive gadgetry can be of help, but they can never be a substitute for sound clinical acumen and experience gathered over years of trials and tribulations. The use of machines and, in particular, of invasive technique, should never be an end in itself, but always a means to the solution of difficult problems. To feed a machine in a critical care unit just because it is there, is to court medical nemesis.

The speciality of critical care by its very nature often incites the caring physician to prompt or hurried action. Admittedly, there are a few emergencies which do demand immediate measures if life is to be salvaged. But in most critical situations, there will be time to stand and wait, to think and deliberate—

"And time for all the works and days of hands
That lift and drop a question on your plate."

The physician must take time to muster the clinical discipline that allows a focused view on an emergent threatening problem, yet not lose an overall perspective of the patient. The initiate in critical care medicine should first and foremost be reminded ever so often of the Hippocratic dictum, *Primum Non Nocere*—first of all, do no harm. He should, therefore, be encouraged to think (without falling asleep) over a problem before jumping into action, else he may well become the prime iatrogenic hazard in the unit.

In the final analysis, critical care is the care that aids and improves patient survival. It is doctors and nurses who care for the patients and not machines. We should take comfort in the fact that there is no substitute for human ingenuity, endeavor and resources. Motivation and dedication toward providing better patient care can indeed compensate significantly in our part of the world for the lack of sophisticated technology and technical expertise.

I very sincerely acknowledge my thanks to all my extremely distinguished contributors who are all well-known specialists in their own fields, and who have so kindly and willingly contributed in an honorary capacity to this book. They have immeasurably enhanced the prestige of this book by their valuable contributors. I would like to acknowledge my immense gratitude most of all to Dr Ruby Jal Kharas, my research assistant, who has made this book her special baby. She has been of immense help in every single aspect of this book, and this book would have had to wait for many more months to see the light of the day, if it had not been for her dedication and perseverance. I also owe an immense debt of gratitude to Mr Oatta, Chairman of Hindustan Lever Ltd, India, who on behalf of his company has been kind enough to give a very generous subsidy toward the publication of this magnum opus. The price of this work has thereby been substantially reduced so that the book is now within the reach of all students and all my medical colleagues. Dr Ramnik Parikh and Dr Rajgopal were instrumental in arranging for this munificent subsidy, and to them I express my sincere gratitude. I would also like to thank the publishers and authors who have granted me permission to reproduce some figures and tables from their books/journals. Although every effort has been made to trace copyright holders of material printed in this book, in some cases, this has not proved possible. In a few cases, the copyright holders are yet to respond. The publishers will be glad to hear from them.

I would also like to thank Dr Shilpa Bhojraj for her assistance with the chapter on Control of Pain and Anxiety and the Use of Muscle Relaxants in the Critically Ill. My special thanks are due to Mrs Lavanya Ray and Ms Rivka Israel for their excellent editorial advice and assistance. I am grateful to Mr Abe Aboody and Mr Balagangadharan of Alliance Phototypesetters for their kind cooperation and excellent work. I am also grateful to Mr V Pradhan and Mr Prabhu for the good art work and X-ray plates. I also offer my thanks to Ms Katy Irani who has helped with the typing of this manuscript and with the Index. My gratitude to my wife, Vera, for having helped to correct the page proofs and for her extra forbearance and care during the many days and nights spent on this work. Finally, my sincere thanks to the Oxford University Press in Mumbai and Delhi for their unstinted help and cooperation in publishing this work.

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SECTION

1

An Introduction to Critical Care

- Overview
- Principles, Philosophy and Ethics of Critical Care
- Critical Care Scoring

CHAPTER 1

Overview

Critical care is the care of seriously ill patients with life-threatening illnesses or trauma, as also of patients who have the potential to develop life-threatening complications from their disease. Critical care should, correctly speaking, be reserved for patients with severe but potentially reversible problems. Patients with chronic terminal illnesses, with the end close at hand should be given every care at home or in the ward of a hospital, but not in critical care units.

The origin of the present day intensive care unit started with the use of the postoperative recovery room for immediate special postoperative care. This concept was given a further impetus during the poliomyelitis epidemic in the early 1950s when the use of mechanical ventilation salvaged many paralyzed patients. Present day intensive care is however far more meaningful than mere postoperative care and ventilatory support. It incorporates the knowledge and experience of numerous specialties that have blossomed over nearly four decades from 1960 onward. Pulmonary medicine with the concept of respiratory care, cardiology with the concept of the coronary care unit and advances in anesthesiology have all contributed greatly to the evolution of the modern day critical care unit. While specialties in medicine or surgery are sharply focused on a single organ system within the body, a general medical or surgical critical care unit is devoted to the patient as a whole, recognizing the overwhelming fact that there is a tremendous interdependence and interrelationship between various organ systems, so that a serious involvement of one strongly jeopardizes the function of others. The approach to critical care medicine is thus simultaneously holistic, viewing the patient in an overall perspective, and yet focused on one or more problems that constitute an immediate threat to life.

It was obvious from the 1960s onward that critically ill patients are best and ideally cared for in special units which centralize equipment, staff and facilities, so necessary for the care of life-threatening problems. Intensive or critical care has blossomed into a specialty with special training and certification in the West, and also in many developed or quickly developing Southeast Asian countries.

In India the seed of critical care planted in the mid and late sixties has now grown into a strong tree trunk with spreading branches and deepening roots. The Indian Society of Critical Care Medicine holds an examination that accredits trained doctors qualified to practice this specialty. These accredited intensivists will in future train junior colleagues, so that the future of this specialty is assured. However, in large cities of the country there are still many privately owned so-called critical care units, which are poorly equipped and poorly staffed. These are death traps for unwary patients. It would be ideal if all units claiming to be intensive (critical) care units have a certificate of accreditation from a responsible professional body.

Many practitioners of critical care medicine are specialists in cardiology, pulmonary medicine, anesthesiology or in critical care itself. However, the principles of critical care are the principles of general medicine and general surgery, rather than the principles applicable to any particular specialty. An individual with a wide experience of medicine or surgery coupled with suitable training and exposure to acute medical or surgical problems has perhaps the best aptitude and philosophy for organizing and directing a critical care unit.

It is important, particularly in a poor country like ours, that the few good critical care units we have, admit patients who truly need appropriate care. It is sad to see critical care

units cluttered with patients who are unquestionably better looked after in the wards or at home. A critical care unit has its advantages and disadvantages. The chief advantage is that it provides better and more organized care. The main disadvantage is of a hostile environment contributing to anxiety, emotional stress, loneliness, fear and above all a greater risk of developing nosocomial infections.

The following conditions require intensive or critical care—

1. Acute life-threatening illnesses which are potentially reversible.
2. Acute illnesses with potential and likely to occur life-threatening complications.
3. Monitoring of vital parameters of patients with symptoms and/or signs that suggest the possibility of an evolving life-threatening illness.
4. Acute or immediate life-threatening crisis or complications in a chronic illness, even when the latter by itself is almost certain to cause death within a matter of months. An example of this is a patient with cancer at a stage when his life expectancy is 3–6 months. An acute complicating pneumonia in such a patient is a life-threatening emergency, which is treatable, curable and may well necessitate critical care.

A critical care unit as already mentioned should not be used for terminal cases where the end is close at hand. The tendency to use a critical care unit as the last halt or stopping station before an expected departure from this world should be strongly deprecated.

This section first deals with the principles and philosophy of critical care. This is followed by a short discussion on ethical principles governing critical care, on ethical issues in terminal illness, and on euthanasia. The section ends with a description of current critical care scoring systems.

CHAPTER 2

Principles, Philosophy and Ethics of Critical Care

INTRODUCTION

The principles of critical care are in quintessence the same as those underlying good medicine and surgery. They include the following—

Early Diagnosis and Identification of the Problem

The doctor in the critical care unit often deals with life-threatening illnesses with serious dysfunction involving one or more organ systems. The early diagnosis and identification of the problem is imperative for correct management. This is a basic dictum for all fields of medicine and surgery but is indeed a matter of urgency in critical care medicine.

Anticipation of Possible Events and Complications

I consider this the very essence of good critical care. The treating doctor must have a firm grip on what is happening to a patient and must acutely anticipate possible events and complications in the immediate future. This he can only do, if he has the knowledge, wisdom and experience of judging the possible evolution of a life-threatening illness in a given patient. To be one step ahead in one's mind with reference to an acutely evolving disease is an important tactical advantage that often leads to victory for the patient and his doctor.

Holistic Approach to a Critical Illness

The holistic approach has already been mentioned earlier. It cannot be overstressed that the patient must be viewed in an overall perspective with interrelated functions of interrelated organ systems. This is not to decry team effort involving various specialists in the management of a critical illness. Team effort is indeed crucial for success, as there is no single physician or surgeon who can know everything, there is to know about the multiple facets of medicine and surgery. Yet, team effort must be conducted and carefully orchestrated by a single individual, if it is to prove successful. Too many specialists and superspecialists individually looking after a critically ill patient more often than not hasten his departure from this world. Their overenthusiastic and often overfocused attention on the organ system of their choice needs to be tempered and viewed with reference to the patient as a whole. The many problems in such patients should be considered in their overall perspective, priority being assigned to those needing immediate attention. Yet it must always be asked as to how best one can engage an emergent problem without seriously jeopardizing the function of other organ systems. A management decision in a not so critically ill patient is often easy and straightforward; a similar decision in a critically ill individual is beset with complex difficulties. The hazards involved in implementing a therapeutic procedure should always be balanced against the possible benefits. There are no clear-cut guidelines in many decisions that need to be made in the care of critically ill individuals. It is a question of experience, wisdom, and at times an intuitive feel of what is probably right or wrong in a given situation.

Considered Use of Technology

The patient is to be cared for by the doctor and the nurses and not by machines. Machines and sophisticated gadgets are an adjunct to the doctor's skill and care; they cannot replace them. Merely because machines have been provided is no reason to use them. Invasive procedures and invasive gadgetry have an inherent risk even in the best of hands; they pose grave hazards in inexperienced or poorly trained hands. Invasive diagnostic procedures may help to fine-tune

management in individual patients, but their overall influence on reducing morbidity and improving mortality in critically ill patients is debatable. It is remarkable that how with increasing experience, the use of invasive monitoring is significantly reduced. Again this is not to decry the use of sophisticated technology in the intensive care unit (ICU). It is merely to restress that in the final analysis, good care rests with doctors and nurses, and not with machines.

Primum Non Nocere

First of all, do no harm. This is an ancient Hippocratic tenet. Do not subject the patient to procedures and investigations which add to pain and suffering, when one is certain or almost certain that these can lead to no extra benefit. The risk-benefit ratio should always be kept in mind in all management decisions in the ICU.

Recognition of the Limits of Critical Care

Physicians involved with critical care must recognize the limits of such care. Critical illnesses are necessarily associated with a high morbidity and mortality, and quite often this morbidity and mortality cannot be improved despite all the care available in present times. The discerning physician learns to recognize the limits of care, knows when to draw the line, and recognizes the futility, and often the cruelty of aggressive management in patients who are well past the point of no return. Learning the limits of care is not easy; it is fraught with doubts, difficulties and danger. A working guideline is to struggle unto life or death in a young individual with a potentially reversible life-threatening illness, and to remember not to play God in the ICU. Yet in the old and feeble, in patients who are clearly dying, and in those with serious background illnesses, one must learn through wisdom and experience to temper care with reason.

CRITICAL APPRECIATION OF EVIDENCE-BASED MEDICINE

Evidence-based medicine is the rallying cry of all modern medicine, a shining banner held aloft by the profession for all to view, a promised trail for better health care and for appropriate management of critically ill patients. It is unquestionably important to judge the clinical effectiveness or otherwise of treatment options through scientifically accumulated evidence. It is even more important to gather evidence to ensure that a treatment option is not injurious to patients. However, in critical care medicine, it may be impossibly difficult and even unethical (in some situations) to furnish evidence or proof as to the optimal approach to acutely emergent problems occurring in very ill patients with many variables. In spite of all protocols and guidelines based on evidence, the practice of critical care medicine today remains largely empirical. The student of critical care medicine should be aware of a few more aspects of evidence-based medicine. Double blind randomized controlled trials are the gold standard, which provide evidence for patient management with regard to a particular problem in critical care. Yet, it must be remembered that the evidence provided, though valuable, is based on a statistical study of large population groups. The results of a statistical study of large population groups, however scientific, need not necessarily apply to the individual patient in one's care. On the other hand, observational studies are considered the weakest form of evidence in critical care medicine. Yet, some of the greatest discoveries in medicine have been made by our illustrious ancestors through the sheer excellence of observation—discoveries far greater than some of the best double blind randomized controlled studies of the present era. Witness the discovery of small pox vaccination by Jenner, antirabies vaccination by Pasteur, the observations of Lister that led to advances in surgery and the observation of the importance of handwashing by Thomas Ignas Semmelweis.

The intensivist should also remember that evidence can be imperfect, can change and is not sacrosanct. If it were, medicine would be static, whereas history teaches us that it is ever-changing, dynamic. It is also possible that the conclusions drawn from evidence-based medicine in the Western world will not always apply to the rest.

Therefore, evidence-based medicine should be viewed in its proper perspective—*good but not infallible, important but not all-inclusive; applicable in many, but not in all. Medicine has several other aspects —social, cultural, economic, psychological, philosophical, religious, genetic, and other nebulous aspects that characterize a trusting caring doctor-patient relationship. It is important to take all into consideration when caring for acutely ill patients.*

CLINICAL JUDGMENT

A physician must be a judge. Judgment is difficult, for indeed medicine has been defined as the art of coming to a conclusion on insufficient evidence. It is no surprise that errors in judgment frequently abound. Clinical judgment does not come within the purview of art or science. It is a special quality, a faculty—often inborn and occasionally cultivated. It cannot be equated to intellectual ability for it may be lacking in brilliant minds and be present to a marked degree in those who are in other respects for less clever or knowledgeable. Perhaps a knowledge of and an interest in the humanities—literature, poetry, music, history, philosophy, religion—can improve clinical judgment by providing a more holistic perspective of man and medicine and of health and disease.

To cope with the diagnosis and management of a life-threatening emergency requires more than mere factual knowledge, reason, logic, experience and skill. It requires good clinical judgment—the hallmark of a good physician. Clinical judgment is a rich blend of all the above requisites and adds to these a further intangible, indefinable quality; a quality that encompasses faith, charity, hope and compassion; a quality that has a deep understanding of human nature. It is also the quality that gives the doctor in crisis the wisdom to know what to say and do, and what not to say and do; when to

wait and watch, and when to treat vigorously without delay; when to fight death and when to give in to it; when to press for a cure and when to console with words, or to rest content with palliative relief. Sound clinical judgment includes an extra-special perceptive ability that enables a doctor to sense a clue which his less fortunate colleagues will miss; the ability to process this clue and judge its correct diagnostic, therapeutic and prognostic implications. A physician who combines the sharpness of his perceptive faculties with a wisdom born of reading and experience, with a compassion for and an understanding of human suffering and who also possesses the faculty of good clinical judgment in truly blessed by the Gods. He has an attribute which no medicine can duplicate and no science can invent. He enjoys a ringside seat in the theater of life and has the most intimate insight into many who seek his help.[1]

ART OF MEDICINE

Today, science rules medicine. However, the practice of its science without an equal measure of its art dehumanizes medicine, robs it of its essence. This is unfortunately the trend today, which must be reversed. The art of medicine lies in the artful, appropriate application of its science to the overall holistic care of an individual patient. The art of medicine remains all pervasive even when its science fails or has reached its utmost limits. "For when all the marvels of science are of no avail to unfortunately ward off the fatal end, it is no small portion of a physician's art to rid his patient's path of thorns if he cannot make it bloom with roses."[1]

The art of critical care medicine lies in hearing an unspoken subtle nuance in a patient's history and in the ability to spot and appreciate the significance of one or more subtle physical signs that no gadget or machine could possibly recognize. It lies in his ability to sift the evidence before him and give the right answer (of several possible answers) to the appropriate question. It lies in the intuitive feel for a solution either in diagnosis or management. Above all, it consists of looking at a very ill patient holistically rather than compartmentalizing the patient into different organ systems. The art of medicine is the art of healing, not just treating, not even just curing. Yet it is only when art and science join hands that healing is best accomplished. It is only then that a physician can engage the unique individuality of a particular human being so that a critically ill patient becomes much more than a disease that needs to be treated.[1]

I came across the ancient description of a good physician and I feel that it has a timeless relevance—"it was his path to learn the practice of medicine and the practice of healing, and careless of fame, to exercise the quiet art".

ETHICAL PRINCIPLES GOVERNING CRITICAL CARE

The principles of ethics are rooted in religious, philosophical and sociocultural traditions. These vary in different cultures and countries, but the absolute values of good and evil, right and wrong, and the sanctity of human life are remarkably similar in all civilized societies.

There are three basic ethical principles derived from these absolute values, which govern the art and science of all medicine, and in particular of critical care medicine. The first is beneficence and its companion-in-arms, nonmaleficence. Beneficence is an all-important ethical principle and duty of the physician, which has been emphasized in ancient Ayurvedic texts, as also by Hippocrates. Beneficence directs the physician to do good by relieving suffering and restoring good health. Beneficence does not merely involve technical expertise and medical skill; it equally involves human qualities, particularly in the care of critical illnesses. It is these human qualities, which tend to be unfortunately forgotten or pushed into the background by the frontiers of advancing technology in medicine. The chief of these human qualities expressed in a single word is humanity. Humanity can be defined as the sensibility, which enables a physician to feel for the distress and suffering of a patient, prompting him to relieve them. True humanity in a physician is the fount of sympathy and care for a critically ill patient. A critically ill but conscious patient in my opinion has special antennae (very like what the child has for the mother), which enable him to promptly recognize, reach out and clasp to his heart a physician who truly cares. This often makes the difference between life and death in a critical illness. In a similar manner, a critically ill individual often recognizes the pseudosympathy exhibited by some physicians; however, brilliant and technologically well-equipped they may be. Knowledge and experience when linked to humanity make a great physician and indeed a great man.

Nonmaleficence is the companion-in-arms of beneficence. It reminds the physician that above all, he should do no harm. Beneficence and nonmaleficence may at times in a critical care setting be in apparent conflict. Thus, the use of a narcotic to relieve pain is beneficence in a dying patient, yet this may hasten death by depressing respiration, thus violating the tenet of nonmaleficence. This conflict, as explained later, is apparent and not real.

The second basic ethical principle governing decision-making and management in critical care medicine is patient autonomy. This is the patient's right to self-determination—the right after being properly informed, to accept or refuse medical treatment offered to him including life support measures like mechanical ventilation. It is indeed the proper interpretation of the balance between the principles of beneficence and the principles of patient autonomy, which governs decision-making and management in critical care medicine. This balance is indeed difficult and not easy to strike in a critical care setting. This is because seriously ill patients may be unable to make proper decisions about their own care. In fact, they may often make the wrong decisions under the physical and emotional stress of their illness. In these circumstances, the physician must lean toward the principle of beneficence, and take management decisions, which he

genuinely believes, are in the best interests of the patient. It is important to illustrate this point with true-to-life examples. A patient was brought in nearly dead after a sedative poisoning, with a note informing the physician that it was her express wish not to be resuscitated and treated. The directive was ignored; the patient was resuscitated and discharged in good health. She was forever grateful for being restored to life.

A patient with quickly progressive respiratory muscle weakness, in his extreme fright, agitation, anxiety and distress, refused intubation and mechanical ventilator support. The request was ignored, appropriate management decisions taken, and the patient was again ever grateful to the doctor for having ignored his directive.

There are many factors which distort, prejudice or interfere with autonomous decisions of patients in critical care medicine. These include fear, anxiety, depression, panic, lack of information and abhorrence of invasive modalities of treatment, which prompt them to decide (often wrongly) to die with dignity. The working ethical principle is that in acute medicine, when confronted with a potentially reversible life-threatening illness, beneficence prevails over patient autonomy.

The third and final ethical principle is justice—to distinguish in patient care, the right from the wrong. If at times this is difficult or impossible to determine in absolute terms, one should determine what is more right or less wrong. In developing countries where resources are limited, justice dictates that treatment is administered to patients who are more likely to benefit from them. This often produces an ethical quandary. Witness for example a situation where there are three ventilators in an eight-bedded tetanus ward and all eight patients have severe tetanus requiring mechanical ventilation. Physicians should unquestionably be involved in the ethics of resource distribution that provide equitable medical care to the society in which they live and work. Yet, ethical arguments limiting care because of limited resources should not in my opinion be applicable to an individual patient already under intensive care. Wisdom however dictates that in all situations requiring protracted intensive care, the burden-benefit relationship should be carefully considered, and care be tempered with reason, when judged to be an exercise in futility.

EUTHANASIA

No discussion of ethics in relation to modern day medicine, including critical care medicine, can be complete without a short discussion on euthanasia. Euthanasia includes—

Voluntary euthanasia or intentional killing of patients who express a competent, freely made wish to die, because of the pain or suffering they experience.

Medically assisted suicide, at the patient's insistence and wish.

Homicide following a surrogate decision on a crippled or handicapped patient, or in a patient with a poor or hopeless quality of life. In this case, the patient is not involved in the decision.

Advocates of euthanasia remarkably enough invoke the ethical principles of beneficence, stating that the act is morally justified because it is doing good to the patient and is in his or her best interest. In my opinion, this act is wrong, unjustifiable, and violates the sanctity of life, as it is perpetrated with known intent to kill. Yet, it must be clearly understood that withholding or withdrawing treatment, when it is certain that such treatment will be of no benefit and when death is inevitable, does not constitute euthanasia (even though some prefer to call this passive euthanasia) because the intent is not to kill but to prevent prolongation of the act of dying.

I gather from discussions with my colleagues in the West, that a significant number of acutely ill patients who are about to die, as also patients with chronic but terminal disease, express a desire to be killed or to be medically assisted in suicide. It is amazing that in my long association of over 45 years with so many critically ill patients in their terminal state, there has not been a single individual who has persistently wished for euthanasia. There have been a few who have expressed a fleeting wish, but talking to them and gently explaining measures to relieve their symptoms have led to a resigned and comparatively unanguished acceptance of their destiny. Why is there this difference between the East and the West? I think it is basically related to sociocultural and religious differences. A patient's, and for that matter a physician's attitude to suffering, pain, impending death, and death itself, is conditioned by these sociocultural and religious factors. Most people in our part of the world and in the Far East believe that life cannot be divorced from pain and suffering, that we live in the midst of pain and suffering, and that each one in this world is apportioned one's share of pain and suffering. This is the law of Karma—a belief that one reaps in the present life what one has sown in previous lives, and that one will reap in future existences what one sows in the present.

In our experience, suffering in a terminal illness (whether this is a sequel to an acute or chronic problem), almost always can be relieved by appropriate medication and compassion. This brings us to the question of whether it is imperative to tell the patient the exact truth that his terminal illness will inevitably end fatally. Here again, East and West may differ. The relatives have a right to know the whole truth, and it is the moral obligation of the physician to apprise them of this truth. Many terminally ill patients either in critical care units or outside, know and feel that their illness is terminal, but barring rare exceptions, they do not wish to discuss death or dying with the physician. In fact, they will if possible, in no uncertain terms stop the physician from broaching the issue. I would agree that the ethical principle of patient autonomy includes the patient's right to know and understand the nature of his illness, so that an informed consent or dissent regarding management decisions is possible. Yet, a patient also has a

right to choose exactly how much he wants to know. If the physician is to exert beneficence, he must respect that right. Perhaps the patient's disinclination to discuss the end is due to a faint glimmer of hope that life will extend longer than what the physician feels or what medical science expects. I am of the opinion that under these circumstances, a physician has no right to systematically destroy that glimmer of hope, which keeps the patient more happy and peaceful toward the end of his life.

To die with dignity and to legalize euthanasia are slogans often linked together, as if one needs the latter to achieve the former. Legalizing euthanasia in our country, even in the most diluted form, could well open the floodgates to murder. Euthanasia however, under strict clauses and safeguards, has already been legalized in Holland. Perhaps in time to come, it may be similarly legalized in other Western countries as well. I am in no position to comment on the Western world, but for all the safeguards and guarantees against misuse that the Dutch for example have, is it not possible that a patient would want to end his suffering as a matter of a cult, or even as a matter of duty that needs to be performed in time to come? Is it ever possible to quantify suffering? Is not suffering often a state of the mind? And cannot a state of the mind be subject to changing social pressures and social mores? Can most doctors claim to have the knowledge, experience, the Ostlerian wisdom and perspective to be truly able to enlist themselves to the cause of euthanasia in a patient who states, I cannot bear the suffering I am going through? These are pertinent questions which are difficult to answer. Finally, when one legalizes a solution to a problem like euthanasia, would the good that accrues clearly outbalance the evil or harm that could possibly result from this legal sanction. This again is a question that physicians all over the world should seriously consider.

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CHAPTER 3

Critical Care Scoring

Optimized distribution of medical and financial resources is of crucial importance in the delivery of health care, particularly in the poor developing countries of the world. To this end, the critical care physician often has to make decisions about which patients are likely to derive the maximum benefit from admission to a critical care unit.

Illness scoring systems have been introduced in the past three decades to formulate some degree of priority for intensive care unit (ICU) admissions in patients with acute illness or trauma. These scoring systems are useful for medical audit purposes and for comparison of therapy and results in groups of patients who roughly have the same degree of physiological derangements produced by critical illnesses. However, scoring systems have strong limitations, and critical care of individual patients should not be influenced by scoring protocols.

The commonly used trauma and critical care scores are briefly discussed below.

GLASGOW COMA SCORE

The Glasgow Coma Score (GCS) judges the extent of coma in patients with head injury. It is useful for pre-hospital trauma triage as also for patient assessment after hospitalization. The scale is based on eye opening, motor response and verbal response (Table 1), and can be tested and scored by the physician within a couple of minutes. The total score is the sum of each response and varies from a minimum of 3 to a maximum of 15. The lower the score the greater the severity of head injury in relation to central nervous system (CNS) function.

Table 1: Glasgow Coma Scale

Eye opening	*Motor response*	*Verbal response*
4 = Spontaneous	6 = Obedient	5 = Oriented
3 = To voice	5 = Purposeful	4 = Confused
2 = To pain	4 = Withdrawal	3 = Inappropriate
1 = None	3 = Flexion	2 = Incomprehensible
	2 = Extension	1 = None
	1 = None	

TRAUMA SCORE AND REVISED TRAUMA SCORE

These are useful for patients with trauma. The trauma score is based on the state of the cardiovascular and respiratory systems and on the GCS (Table 2). Values are given to each parameter and these are added to give the total trauma score, which ranges from 1 to 16. The lower the score the greater the risk for mortality.

The trauma score was found to underestimate the prognostic significance of head injuries. This led to the development of the revised trauma score (RTS), which is now widely used to assess the severity of trauma. The RTS is based on the GCS, the systolic blood pressure (SBP) and the respiratory rate. Coded values are given for the above parameters and summed up (Table 3). Higher values have a better prognosis and lower values a poor prognosis.

CRAMS SCALE

The circulation, respiration, abdomen, motor, speech (CRAMS) scale is another trauma triage scale frequently

Table 2: Trauma score

A. Systolic blood pressure	*B. Respiratory rate*	*C. Respiratory effort*	*D. Capillary refill*
>90 4 70–90 3 50–69 2 <50 1 0 0	10–24 4 25–35 3 >35 2 <10 1 0 0	Normal 1 Shallow or retractions 0	Normal 2 Delay 1 None 0
E. Glasgow Coma Scale			
1. *Eye opening* 4 = Spontaneous 3 = To voice 2 = To pain 1 = None	2. *Motor response* 6 = Obedient 5 = Purposeful 4 = Withdrawal 3 = Flexion 2 = Extension 1 = None	3. *Verbal response* 5 = Oriented 4 = Confused 3 = Inappropriate 2 = Incomprehensible 1 = None	(1 + 2 + 3) 14–15 5 11–13 4 8–10 3 5–7 2 3–4 1
Trauma score (A + B + C + D + E) = _____			

Table 3: Revised trauma score (RTS)*

Glasgow Coma Scale (GCS)	*Systolic blood pressure (SBP) (mm Hg)*	*Respiratory rate (RR) (breaths/min)*	*Coded value*
13–15	>89	10–29	4
9–12	76–89	>29	3
6–8	50–75	6–9	2
4–5	1–49	1–5	1
3	0	0	0

*RTS = 0.9368 GCSc + 0.7326 SBPc + 0.2908 RRc, where the c refers to coded value.

used to decide which patients require urgent admission to a trauma unit (Box 1). Patients with a low CRAMS score need urgent critical care.

INJURY SEVERITY SCORE

This system assigns numerical scores to different body regions that may be injured. A manual of codes provides information on the scoring of each injury. The worst injury in each region is given a numerical value. This is squared and added to numerical values from each of the other anatomical regions. The total score ranges from 1 to 75 and correlates with the mortality risk. The injury severity score (ISS) has some important limitations. It considers only the highest score from each body region, and considers injuries with equal scores to be of equal importance irrespective of the anatomical region injured. The ISS is frequently used as a measure of overall trauma, and forms a rough guide to mortality risk in the injured patient.

Box 1: CRAMS scale*

Circulation—
- Normal capillary refill and blood pressure (BP) >100 mm Hg 2
- Delayed capillary refill or 85 < BP < 100 mm Hg 1
- No capillary refill or BP <85 mm Hg 0

Respiration—
- Normal 2
- Abnormal (labored or shallow) 1
- Absent 0

Abdomen—
- Abdomen and thorax nontender 2
- Abdomen and thorax tender 1
- Abdomen rigid or flail chest 0

Motor—
- Normal 2
- Response to pain (other than decerebrate) 1
- No response (or decerebrate) 0

Speech—
- Normal 2
- Confused 1
- No intelligible words 0

*Score <8 indicates major trauma; score >9 indicates minor trauma.

ACUTE PHYSIOLOGY, AGE, CHRONIC HEALTH EVALUATION

The acute physiology, age, chronic health evaluation II (APACHE II) score is one of the most frequently used critical

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scales in critical illnesses. It is used in order to stratify prognosis and outcome in groups of patients, and to determine success of different forms of treatment.[1-6] The APACHE II score uses twelve easily measured variables [Acute Physiology Score (APS)] and takes into consideration background disease or premorbid health (Table 4). The worst scores in the first 24 hours following ICU admissions are used. The twelve parameters considered are—

1. Temperature (°C).
2. Mean arterial pressure (MAP) (mm Hg).
3. Heart rate (beats/min).
4. Respiratory rate (breaths/min).
5. Alveolar-arterial oxygen gradient (A-aDO_2) if fractional inspired oxygen (FiO_2) is 0.5 or greater, or PaO_2 if FiO_2 less than 0.5.
6. Arterial pH.
7. Serum sodium (mmol/L).
8. Serum potassium (mmol/L).
9. Serum creatinine (mg/dL).
10. Hematocrit (%).
11. Leukocyte count (cells/mm^3).
12. Glasgow Coma Score.

Depending on the degree of derangement, a weighted score is given to each parameter. Sedated, ventilated patients are given a GCS of 15 when neurological problems seem unlikely.

Scores are also assigned for increasing age, emergency postoperative or nonoperative admission, and for the presence of background diseases resulting in pre-existing organ dysfunction. Double weighting is assigned to derangements of serum creatinine in the setting of acute renal failure, due to marked increase in mortality in critically ill patients with

Table 4: APACHE II points (A + B + C below)

A. Acute Physiology Score (APS)									
Physiological variables	*High abnormal*			*Normal*			*Low abnormal*		
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature rectal (°C)	≥41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9
MAP (mm Hg)	≥160	130–159	110–12		70–109		50–69		≤49
Heart rate (beats/min)	≥180	140–179	110–139		70–109		55–69	40–54	≤39
Respiratory rate (breaths/min)	≥50	35–49		25–34	12–24	10–11	6–9		≤5
(A-aDO_2) mm Hg if FiO_2 ≥0.5	≥500	350–499	200–349		<200				
PaO_2 mm Hg if FiO_2 <0.5					>70	61–70		55–60	<55
Arterial pH	≥7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
Sodium (mmol/L)	≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110
Potassium (mmol/L)	≥7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5
*Creatinine (mg/dL)	≥3.5	2–3.4	1.5–1.9		0.6–1.4		<0.6		
Hematocrit (%)	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
Leukocytes (cell/mm^3)	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1
Neurological points = (15-Glasgow Coma Score)									
B. *Age Points*	Age ≤44 0 point		45–54 2 points		55–64 3 points		65–74 5 points		≥75 6 points
C. *Chronic Health Points*	2 points for elective postoperative admission 5 points if emergency operation or nonoperative admission, if patient has significant chronic liver, cardiovascular, respiratory or renal disease or is immunocompromised								

*Points are doubled in acute renal failure.

Abbreviations: MAP, mean arterial pressure; A-aDO_2, alveolar-arterial oxygen gradient; FiO_2, fractional inspired oxygen.

acute renal failure. The maximum possible APACHE II score is 71. Increasing scores correlate with increasing mortality at each 5-point increment across a wide range of diseases.

The APACHE II scoring system is a useful scale in critical care medicine. Nevertheless, it is wrong to allow APACHE II scores to influence management in individual patients. A high initial APACHE II score in postoperative coronary artery bypass surgery is not necessarily associated with a high mortality.[6] It is also shown later in this book (see Chapter Multiple Organ Dysfunction Syndrome) that tropical problems may be associated with severe multiple organ dysfunction (and high APACHE II scores), and yet do not have the grim prognosis forecast by the APACHE II score. A critique of these scoring systems is given in the Chapter Multiple Organ Dysfunction Syndrome.

Several variants of the APACHE II scoring systems have been devised. These include Bion's sickness score,[7,8] mortality prediction models[9-11] and the therapeutic intervention scoring system.[12,13]

None of these scoring systems have any significant advantage over the more frequently used APACHE II score, and none of these should significantly influence decision-making in individual patients. There is also little or no difference in the predictive ability of each of these systems over a wide range of scores.[11]

The APACHE II scoring system (and its modifications) was not designed to judge individual patient outcomes. A new scoring system (the APACHE III score) has been introduced to objectively assess patient risk for death and other important outcomes related to patient stratification. This new system aims to provide (1) an APACHE III score; (2) a series of predictive equations that help to predict individual patient mortality at different times during the patient's stay in the ICU.

The APACHE III system is based on seventeen physiological variables or parameters, and includes within its ambit a coma scale, age and pre-existing comorbid conditions.[14] The APACHE III score is calculated by adding the coded variables for each category. A 5-point increase in the APACHE III score (range 0–299) is associated with increased risk of death. Further use and evaluation of this scoring system is necessary before it can be used routinely for triage decisions in critical care.

OTHER IMPORTANT SCORING SYSTEMS IN CRITICAL CARE

In the 1990s three other important scoring systems were devised to predict the outcome in critically ill patients. These were: (1) the sequential organ function assessment (SOFA) score, (2) the multiple organ dysfunction score and (3) the simplified acute physiological score I (SAPS I); this was further modified to SAPS II. Unlike the APACHE II scoring system, which is used only on admission of the patient to the ICU, the SOFA score, multiple organ function score and SAPS II score are determined daily in a critically ill patient till either recovery or death occurs. These scoring systems take into consideration two obvious facts: (1) organ dysfunction is a continuum, varying from very mild at one end of the spectrum to hopelessly severe at the other end; (2) organ dysfunction is a dynamic process and the degree of dysfunction or failure could vary with time.

Sequential Organ Function Assessment Score

The SOFA score is made up of scores from six organ systems graded from 0 to 4, depending upon the degree of dysfunction.[15] A SOFA score greater than 15 is associated with a mortality greater than 80%.[16] We use this scoring system in our unit and find it valuable. However, as explained in the Chapter Multiple Organ Dysfunction Syndrome, we have noted that in fulminant tropical infections (e.g. falciparum malaria), high SOFA scores do not necessarily predict death. The recovery rate in these infections is significantly higher than that predicted by the SOFA score (see Chapter Multiple Organ Dysfunction Syndrome). Table 5 gives the details of organ function assessment through the SOFA system.

Multiple Organ Dysfunction Score

The multiple organ dysfunction score was devised because of the direct relationship between the number of organs that fail to mortality in ICU patients.[17] The score for each patient is assessed daily, allowing a better prediction of morbidity and mortality (Table 6).

Simplified Acute Physiology Score

The SAPS I score was developed from a small database of about 700 patients in France, as a simplification of the APACHE scoring system.[18] The SAPS I score had a range from 0 to 56 and was based on physiological parameters, age and invasive or noninvasive ventilation. Predictive results using the SAPS I were found to be comparable to those using the APACHE I score. The main drawback of the SAPS I as an outcome prediction tool was that it did not take into consideration the specific diagnosis and background diseases or chronic health status of the individual.

About a decade later, the updated SAPS II score was developed from a large database of more than 13,000 patients from ICUs across Europe and North America.[19] The SAPS II score is calculated using seventeen variables—twelve physiological parameters, age, type of admission (emergency/elective), presence of acquired immunodeficiency syndrome (AIDS), metastatic cancer or hematologic malignancy. The main outcome measure predicted by the SAPS II is vital status at hospital discharge. It has been found to perform better than SAPS I and its performance is comparable to that of the APACHE II. Modifications of the SAPS II have been used to make it more applicable at local ICU levels and also for clinical trials in specific diseases and conditions such as sepsis.

The SAPS III is developed by the European Society of Intensive Care Medicine. The database for this score is expected to be very large, collected from ICUs all over the world. The SAPS III will consist of four modules: (1) a basic

Table 5: Sequential organ failure assessment (SOFA) score

	0	*1*	*2*	*3*	*4*
Respiration— • PaO_2/FiO_2	>400	≤400	≤300	≤200 with ventilatory support	≤100 with ventilatory support
Coagulation— • Platelets ($\times 10^3/mm^3$)	>150	≤150	≤100	≤50	≤20
Liver— • Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular— • Hypotension	No hypotension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any dose)*	Dopamine >5 or epi ≤0.1 or norepi ≤0.1*	Dopamine >15 or epi >0.1 or norepi >0.1*
Central nervous system— • Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal— • Creatinine (mg/dL) • Urine output	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500 mL/day	>5 or <200 mL/day

*Adrenergic agents administered for at least 1 hour (doses given are in µg/kg/min).
Abbreviations: FiO_2, fractional inspired oxygen; MAP, mean arterial pressure; epi, epinephrine; norepi, norepinephrine.

Table 6: Multiple organ dysfunction score

	Points				
	0	1	2	3	4
PaO_2/FiO_2	>300	226–300	151–225	76–150	≤75
Serum creatinine (µmol/L)	≤100	101–200	201–350	351–500	≥500
Serum bilirubin (µmol/L)	≤20	21–60	61–120	121–240	>240
Pulse-adjusted heart rate*	≤10	10.1–15	15.1–20	20.1–30	>30
Platelet count (× 103/dL)	>120	81–120	51–80	21–50	≤20
Glasgow Coma Score†	15	13–14	10–12	7–9	≤6

*PAR = HR × (RAP/MAP); HR, heart rate; RAP, right atrial pressure; MAP, mean arterial pressure.
†The best estimate in the absence of sedation.
Scoring method: The most abnormal value for each parameter over a 24-hour period is selected for scoring purposes. The addition of scores of all six parameters gives the final score. It has been observed that scores between 13 and 16 carry a 50% mortality, scores between 17 and 20 carry a 75% mortality and scores >20 carry a 100% mortality.

evaluation module, (2) an extended outcomes module, (3) an infection module and (4) a resources module. Along with predictive models for patient outcomes, the score is also expected to provide a reliable tool for evaluation of individual ICUs with a special emphasis infection rates and cost-benefit ratios of investigations and therapies.

CRITICAL CARE SCORING IN THE FUTURE

The evolution and practice of better future scoring systems need to take into account: (1) factors which predict patient outcome, (2) effectiveness of therapy or management and (3) efficiency of delivered care.

Critical care is however a complex process. Patients receiving critical care constitute many variables related to different disease processes. The problem is further compounded by the fact that delivery of critical care in different parts of the world is influenced by cultural, social and economic factors. For these reasons, it is difficult to quantify critical care with measurable values and compare these values with different institutions in different countries of the world.

Present scoring systems are a valuable guide to patient outcome and indirectly on how management can affect outcome. Yet, it is our opinion that scores should not influence management decisions in individual patients. Clinical judgment should never be replaced by any scoring system or scale.

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SECTION

2

Cardiopulmonary Resuscitation and Cerebral Preservation in Adults

- Cardiopulmonary Resuscitation and Cerebral Preservation in Adults

CHAPTER 4

Cardiopulmonary Resuscitation and Cerebral Preservation in Adults

GENERAL CONSIDERATIONS

A sudden unexpected cessation of effective cardiac pump function or beating of the heart is termed as cardiac arrest. This may be reversible if promptly managed, but otherwise invariably leads to death. Cardiac arrest quickly results in a respiratory arrest and resuscitation therefore involves establishing an effective stable circulation as well as maintaining effective ventilation. Similarly, respiratory arrest if unattended leads within a few moments to cardiac arrest, illustrating the inseparable link between the heart and the lungs. The approach to cardiopulmonary resuscitation (CPR) is therefore always an integrated one directed both to the heart and the lungs. One should in the same breath also consider cerebral preservation, because cessation of effective cardiac pump function results in severe hypoxia due to stoppage or markedly inadequate blood supply to all important organs of the body, most importantly to the brain and the heart muscle itself. Hypoxic brain damage and death therefore always result if resuscitation is delayed, is not implemented or is unsuccessful. In fact, for several reasons brain damage can result even after successful resuscitation. The preservation of brain function (cerebral preservation) during and after CPR is therefore crucial to allow a meaningful quality of life.

It is not the purpose of this chapter to enumerate the numerous causes of sudden cardiac arrest or cardiac death. Ischemic heart disease (IHD) remains the commonest cause in Western countries as also in India. In the sixties, 12% of all natural deaths in the United States of America were sudden, and 88% of all sudden natural deaths were due to cardiac causes.[1] A prospective study in the same country demonstrated that 50% of all coronary heart disease deaths are sudden and unexpected and occur within 1 hour of the onset of symptoms.[2] Cardiac arrest is a dreaded complication during surgery and anesthesia; it can also complicate investigational procedures—pleural, peritoneal or pericardial paracentesis, intravenous (IV) pyelography, cardiac catheterization and coronary or cerebral angiography. It can occur as a consequence of electrolyte and metabolic abnormalities, or may be caused by drugs—particularly antiarrhythmic drugs like quinidine, procainamide and digitalis. It is an important cause of death following trauma, blood loss, asphyxia (due to drowning, carbon monoxide poisoning, and inhalation of food or vomit), sudden large airways obstruction by a foreign body, and electrocution either by electric shock or lightning.

Closed chest compression in the management of cardiac arrest was introduced in 1960. Between 1960 and 2000 there was no change in the long-term survival after cardiac arrest. Evidence accumulated over the last decade has stressed on special aspects of emergency management responsible for successful resuscitation. Also, the importance of specific and meticulous intensive care after successful resuscitation is being increasingly recognized as being crucial to the prevention of brain damage and preservation of cerebral function.

An integrated approach to appropriate emergency resuscitation and postresuscitation intensive care has resulted in improved final outcomes and increased meaningful survivals.

This chapter briefly mentions the epidemiology and the basic mechanisms underlying cardiac arrest. It next describes the various aspects of emergency management of CPR as currently advised. It then deals with post-arrest care directed specifically towards preventing or minimizing brain injury. It ends with a brief discussion of neurological sequelae that can unfortunately occur even after successful resuscitation

and the prognosis of neurological recovery (after restoration of the circulation) based on clinical examination.

EPIDEMIOLOGY

It would be appropriate to state that for several reasons, very little is known about the epidemiology of cardiac arrest in our country. An out-of-hospital arrest in large cities of India is invariably fatal. For one there are very few lay people trained in basic life support and for another it may take hours (because of horrendous traffic) for an out-of-hospital arrest to reach a hospital.

In Western countries, the incidence of out-of-hospital arrests is estimated at 52.1 per 100,000 people per year with a reported median survival rate of 8.4%.[3] The incidence of in-patient hospital arrests is estimated at about 0.17 events per hospital bed per year,[4] survival to hospital discharge being just 17%. It is of note that 17% of episodes of respiratory arrest or compromise may progress to cardiac arrest.[5]

Only 44% of patients who suffer an arrest in the hospital have return of circulation and 60% of those resuscitated from cardiac arrest in hospital die prior to discharge from hospital.[4] Post-ischemic brain injury and multiorgan failure are the causes of these deaths. Failure to awaken contributes to withdrawal of care in Western countries in as many as 24–68% of patients after initial successful resuscitation.

BASIC MECHANISMS

The mechanisms underlying cessation of effective cardiac pump function, which if uncorrected lead to rapid loss of consciousness and death are—

- Ventricular fibrillation (VF).
- Ventricular tachycardia (VT) resulting in pulselessness and an unconscious state.
- Cardiac standstill or asystole; a markedly severe brady-arrhythmia has well-nigh the same effect as an asystole or standstill.
- Pulseless electrical activity (PEA) In this condition, though the electrocardiogram (ECG) or cardiac monitor show a normal or satisfactory electrical activity, the mechanical pumping action of the heart is either feeble or absent.

OBJECTIVES AND PRINCIPLES OF MANAGEMENT

- The chief objective is to restore and maintain stable, effective cardiopulmonary function resulting in effective transport of oxygen to the tissues of the body.
- To prevent or minimize brain damage not only during CPR but also after successful restoration of the circulation.
- Since irreversible brain injury or death can occur within 4–6 minutes of the onset of arrest, immediate treatment is mandatory. *Time is of essence and every single second counts.*
- A preplanned, well-organized management protocol is essential. Initially, it aims at Basic Life Support. In a hospital, particularly in an intensive care unit (ICU) setting, this graduates seamlessly almost pari passu to Advanced Cardiac Life Support.
- There is a window of approximately 4 minutes from the cessation of effective cardiac function (with absence of major pulses) and of respiration, after which hypoxic injury to the brain progresses rapidly, leading to irreversible death. Resuscitation attempts after 10–15 minutes of arrest have rarely been found to be successful, and most doctors hesitate to resuscitate when more than 10 minutes have elapsed after an unattended cardiac arrest. Permanent brain damage and a vegetative state are the sequelae even if the CPR is successful.
- Cardiopulmonary resuscitation in terminal malignancy or in terminal hepatic, renal, or pulmonary diseases offers a cruel extension of life for a short span, and should be avoided. The ethical issues involved are fairly clear, but should be decided in consultation with the patient's relatives, and one's own colleagues.

Management of the Individual Patient

The following steps are detailed for the management of the individual patient (Flowchart 1). In an in-hospital setting, and more so in an ICU setting, one step dovetails into the next, and more often than not, many steps are in simultaneous operation. It is important that in an ICU setting each doctor, nurse or paramedical person knows exactly what is expected of him or her, and that there is one individual to supervise and direct operations.

Recognition of Cardiac Arrest

A health-care provider (doctor, nurse, paramedical person) should assume that a person is in cardiac arrest if he or she is unresponsive and has abnormal breathing. Since prompt and continuous chest compression is of utmost importance, searching for the pulse should never be a lengthy process. Health-care providers, and this includes trained intensivists should spend a maximum of 10 seconds searching for the carotid or femoral pulse. If a definite pulse is not detected, chest compression should start immediately.[6,7]

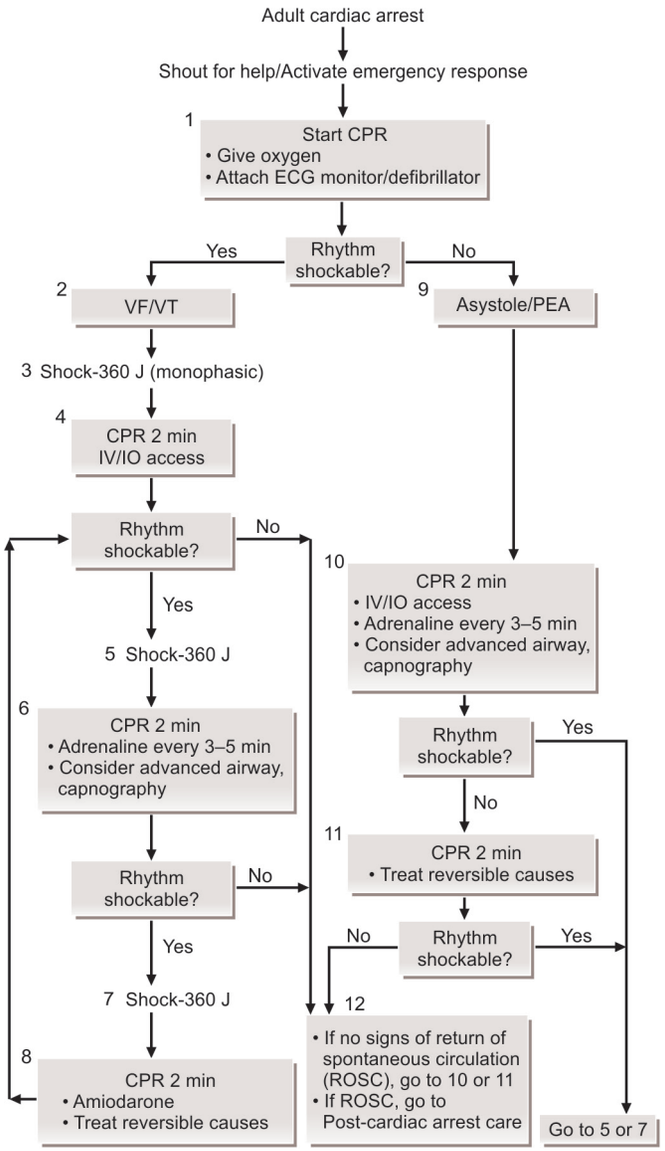
Lay people are instructed not to attempt to feel the pulse. They should assume cardiac arrest if the patient is unresponsive and has abnormal breathing and start chest compressions promptly.

Once a cardiac arrest is diagnosed in hospital and in the wards, the rescuer should promptly shout for help. There should also be a provision for an alarm that summons prompt help. This of course is unnecessary when an arrest occurs in the ICU where prompt help from two or more doctors together with nurses and paramedical personnel is always available.

Restoring Circulation

Restoring circulation is of crucial importance in CPR. This is specifically achieved by prompt uninterrupted well performed chest compressions. Chest compressions augment both the coronary and the cerebral circulation. Interruption in chest

Flowchart 1: Steps in adult cardiopulmonary resuscitation



Source: Adapted with permission from Adult Basic Life Support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 122.

compressions or incorrectly performed chest compressions strongly jeopardizes recovery, leading to a less favorable neurological outcome. In patients who suffer an arrest due primarily to a cardiac cause, chest compressions take precedence over ventilation. In patients who have experienced a primary pulmonary arrest rescue breathing should be started as soon as possible after commencement of cardiac compressions.

In 2010, the American Heart Association (AHA) drastically revised its guidelines for emergency CPR and emergency cardiovascular care.[8] This revision was based on research contributing to improved morbidity and mortality associated with cardiac arrest. Prior to 2010, the basic life support advocated was airway, breathing, circulation (ABC) in that order. The current 2010 guideline is circulation, airway, breathing (CAB) in this new order. The stress first and foremost is now rightly placed on the prompt restoration of circulation by immediately starting chest compressions. Delay in starting of chest compressions is thereby minimized. Care-givers who hesitate or are fearful of performing rescue breathing can start resuscitation more promptly and continue uninterruptedly if they are required to perform chest compressions as their first and immediate task. Another equally important aid in the restoration of circulation is the use of cardioversion and defibrillation in appropriate conditions. The current guidelines also advise on the use of drugs such as epinephrine, vasopressors, dopamine, atropine, antiarrhythmic, and other drugs. They do not however lay great emphasis on these medications, perhaps because they have not been shown to influence outcomes. On the other hand, prompt recognition of VF and prompt defibrillation is life-saving so that defibrillation in a number of patients is second in importance only to chest compressions. Unfortunately, in the large metropolitan cities of India, an out-of-hospital arrest can only be managed by cardiac compressions either by a layperson or by a doctor who happens to be present. The paucity of cardiac ambulances, the time taken by the ambulance to reach the victim, make timely availability of a defibrillator extremely unlikely. Invariably by the time an out-of-hospital arrest reaches hospital, meaningful recovery is extremely unlikely.

An in-hospital arrest, in the wards or in a department or during transfer of a patient from the ward to a department poses special problems. Chances of recovery are increased if there is an organizational system and a protocol that allows rescuers within the hospital to reach the victim as quickly as possible. This aspect is discussed later in the chapter. *However, in an ICU, features of basic life support and advanced life support are seamlessly dovetailed. This is because emergency equipment is waiting and ready* for use, and there are two or more rescuers attending to the crisis. One continues with chest compressions, the other handles the airway and ventilation, a third is ready if needs be to use the defibrillator and a nurse helps to gain access to one or more large peripheral veins in preparation for infusion of drugs.

This chapter will now discuss details of resuscitation of the circulation through closed chest compression and the appropriate use of defibrillation. It next discusses the care given to the airway and breathing and then deals with drugs that may help to restore circulation. Finally, there is a discussion on the post-arrest care (i.e. care after successful CPR). Specialized intensive post-arrest care is necessary chiefly to prevent or minimize brain damage and also to prevent damage to other organ systems.

Basic Life Support consists of—

- Continuous correctly delivered closed chest compressions at 80–100/minute.
- Defibrillation of the heart in patients with pulseless VT or VF.

- Ensuring patency of the airway (head-tilt, chin-lift maneuver).
- Ventilation (mouth-to-mouth or bag-mask ventilation) the ratio of chest compression to ventilator breaths being 30:2.

Advanced Life Support consists of—

- A combination of closed chest compressions and defibrillatory shocks for pulseless VT or VF.
- Securing IV access.
- Advanced Airway Management and Ventilatory Support.
- Pharmacological therapy—epinephrine, inotropes, vasopressors, antiarrhythmic drugs, atropine, and other drugs.

Closed Chest Compressions

Adequate perfusion of the heart (through the coronary circulation) and of the brain (through the cerebral circulation) is vital for meaningful survival. Chest compressions achieve this by building and maintaining coronary and cerebral perfusion pressures.[7,9] The coronary perfusion pressure is quantified by the pressure gradient between the aorta and the ventricular cavities (usually approximated by the central venous pressure or the pressure in the right atrium). Measurements of coronary perfusion pressure are not possible unless the patient has invasive monitoring devices (such as a central venous catheter) before the cardiovascular collapse. With mechanical compression of the chest, cerebral blood flow occurs during this phase of actual chest compression. However, the perfusion of the myocardium through the coronaries occurs during the relaxation phase. Coronary perfusion pressure (which is maximum at the end of the relaxation phase) is strongly correlated with myocardial perfusion and hence with the likelihood of successful resuscitation.[10] It has been estimated that in humans the coronary perfusion pressure should exceed 15–20 mm Hg for successful resuscitation. It is likely that a lesser degree of coronary perfusion pressure is unable to supply adequate nutrients and energy to the myocardium to allow recovery following cardiac arrest.

Position of the Patient and the Rescuer

Proper positioning of the care-giver and the patient is fundamental. In an out-of-hospital scenario, the care-giver kneels perpendicularly to the patient's torso. For the in-hospital cardiac arrest, the doctor or the rescuer should stand at the bedside at the level of the torso of the patient. A soft mattress defeats the very purpose of mechanical cardiac compressions as the mattress absorbs a great deal of the force exerted during compression. If the patient is on an air mattress, it should be promptly deflated.

Compression Technique

Place the heel of one hand on the lower half of the sternum and then place the heel of the other hand over the top of the first. In adults, depress the sternum with a downward force (the down stroke), for at least 2 inches and allow of proper recoil (the upstroke) before starting the next compression. The time for compression and recoil should roughly be equal, the chest being seen to re-expand fully before the next compression. The hands should be slightly removed (lifted) from the chest wall during the upstroke to ensure full and adequate recoil. Interruption of the recoil or inadequate recoil leads to increased intrathoracic pressures and a poor hemodynamic profile characterized by decreased coronary perfusion pressure, poor myocardial blood flow, decreased cardiac index and reduced cerebral blood flow.[11,12]

The recommended rate of delivery of chest compressions is at least 100/minute. The number of delivered compressions per minute is a predictor of return of spontaneous circulation (ROSC) and neurologically intact survival.[13,14] The best outcomes have been observed with at least 80 chest compressions per minute in in-hospital arrests and 68–89 compression per minute in out-of-hospital arrests.[13] It was believed earlier that external chest compression maintained circulation as a result of a squeeze or pressure on the heart between the sternum and the thoracic spine. This squeeze pushed blood out into the systemic and pulmonary circulations, followed by a filling of the heart when the pressure was released. The current concept is that external pressure on the chest leads to an increased intrathoracic and intrapleural pressure, and this positive pressure is responsible for propelling the blood forward. Release of external pressure leads to a fall in the intrathoracic and intrapleural pressures, allowing blood to fill the heart. This thoracic pump theory claims that the entire thorax acts as a pump to propel blood forward, possibly by reducing the afterload of the left ventricle. Afterload can be defined as the peak systolic transmural pressure, and increased intrathoracic pressure would reduce this transmural pressure, thus reducing the afterload, and promoting emptying of the ventricles.

The general guideline for compression to ventilation ratio is 30 chest compressions to two ventilations if there is a single rescuer. If there are two, then one rescuer can administer uninterrupted chest compressions while the other delivers ventilation (see later discussion) keeping the chest compression to ventilation ratio at 30:2. It is crucial not to waste time by inserting an artificial airway at the start of resuscitation as this significantly interrupts chest compression. An advanced airway should be inserted at least 3 minutes after uninterrupted chest compression and after attempted defibrillation, if this is found to be necessary.

Problems Preventing Effective Chest Compression

Chest compressions should start promptly and be delivered continuously with the right technique so as to maintain effective coronary and cerebral perfusion pressure. Even a short pause results in a sharp fall in the coronary and cerebral circulation pressures.[15] It has been noted that interruption in chest compressions are common, consuming 24–57% of the total resuscitation time.[16,17] It has also been noted that chest compressions must be continuous if they are to reach a threshold for successful defibrillation and

resuscitation[18] and counter the brain's extreme vulnerability to ischemic injury.

The following factors encroach upon and can significantly interrupt compression time—

- *Advanced Cardiac Life Support interventions (ACLS)* These can result in numerous pauses in chest compression. The insertion of artificial airways is observed to be responsible for 25% of all interruptions with a median duration of 2 minutes. Endotracheal intubation should not be attempted at the very start of resuscitation. It should preferably await restoration of the circulation or if deemed imperative should be attempted only after 3–5 minutes of continuous chest compression.
- *Frequent Pulse Checks form another Source of Interruption* Pulse check should not exceed 10 seconds; frequent pulse checks are not necessary and should be avoided unless there is other evidence of return of spontaneous circulation (ROSC), such as an increase in the patient's oxygen saturation as measured by an oximeter or an increase in the end tidal CO_2 ($EtCO_2$) measurement. Studies have shown that the patients with ROSC had a mean increase of 10 mm in the $EtCO_2$ as compared with patients with cardiac arrest who failed to survive. $EtCO_2$ measurement can therefore monitor ROSC, obviating the need to interrupt chest compressions.
- *Defibrillation* It is another often necessary procedure which interrupts chest compression. This interruption even while preparing for defibrillation leads to a sharp drop in the coronary perfusion pressure. Till recently the traditional method for defibrillation was to stop compression, analyze the ECG rhythm, charge the defibrillator and deliver the shock to the patient. This amounts to be an interruption of about 15 seconds. The correct method is to charge the defibrillator in anticipation of shocking the patient, chest compressions being continued throughout and being interrupted only during rhythm analysis and delivery of the shock. The average interruption time for chest compressions is thereby close to just 4 seconds. If rhythm analysis show that defibrillation is not warranted chest compressions are promptly restarted, thereby further saving on interruption time. Recent studies have shown that it is completely safe for a care-giver wearing standard examination gloves to continue chest compressions during the use of a biphasic defibrillator with self adhesive pads.[19] There is no danger of an electric shock to the rescuer with biphasic defibrillators in contrast to the legitimate fear with the use of monophasic defibrillators.
- Rescuer fatigue can result in imperfect technique of chest compression. The depth and even the frequency of chest compression may be compromised. A shallow depth fails to generate an adequate coronary and cerebral perfusion pressure. It is also associated with an impaired recoil which results in a reduced coronary artery blood flow and an increased intrathoracic pressure.

More often than not a rescuer fails to recognize or admit fatigue. Ideally, care-givers (i.e. rescuers) giving chest compressions should rotate every 2 minutes. This switch should be seamless the second rescuer being ready and in position on the other side of the patient when the first rescuer is relieved.

Hands-only Cardiopulmonary Resuscitation

If there is a single rescuer there is necessarily an interruption in chest compressions since he or she needs to deliver two rescue breaths after every 30 chest compressions. The performance of a hands-only CPR allows a single rescuer to focus solely on continuous uninterrupted chest compressions. It is believed that ventilation is not necessary in the first few minutes of resuscitation because blood oxygen levels remain adequate for some minutes after a cardiac arrest from a non-respiratory cause.[8] The safe and acceptable duration of oxygen levels in such circumstances is not known. However, chest wall recoil may provide some degree of ventilation and oxygenation during hands-only CPR.

It should however be noted that the hands-only CPR concept contradicts the early work demonstrating that airways collapse in most comatose patients, so that compressions alone cannot provide adequate ventilation.[20] Recent studies suggest that chest compressions generate tidal volumes less than the physiological dead space.[21]

Alternative Cardiopulmonary Resuscitation Techniques

Alternative techniques of CPR have been tried and described with uncertain success.

- High frequency chest compressions are delivered at a rate of greater than 120/minute. Two clinical trials showed improved hemodynamic profile but no improvement in outcome.[22]
- *Open cardiac chest CPR* Direct cardiac massage is resorted to in patients suffering cardiac arrest during thoracic or cardiac surgery as also in patients undergoing other surgery where closed chest compressions have been ineffective. Open chest CPR with direct cardiac massage is also used after cardiac arrest from a traumatic chest injury.

Open cardiac massage (which was the only method to treat cardiac arrest before 1960) has now been supplanted by closed chest compressions. At present, its main use is when the chest is already opened at surgery or when cardiac arrest occurs soon after thoracotomy or occasionally after a laparotomy (if prompt resuscitation through closed cardiac compression is unsuccessful). It should be noted that direct cardiac compression via a thoracotomy procedure produces roughly a threefold increase in coronary perfusion pressure compared to external chest compressions. Also VF and mechanical activity of the heart are directly visible so that direct defibrillation of the heart or direct ventricular pacing can be promptly used if necessary. Finally, cardiac tamponade causing arrest can be promptly relieved by pericardiotomy.

- Interposed intra-abdominal compression (IAC) is another procedure reported to help increase coronary and cerebral perfusion. It requires three rescuers (health care workers). The first provides chest compression; the second compresses the abdomen (with the same hand position and to the same depth) between the xiphoid process and the umbilicus during chest wall recoil. The third provides ventilation preferably with an advanced airway device. IAC results in improved coronary perfusion. An in-hospital trial demonstrated improved survival compared to CPR.[23] A further study is needed to validate this result.
- *A precordial thump* A precordial thump is a forceful blow to the anterior chest wall. It can occasionally stun the myocardium and convert VF or a pulseless VT into a more stable rhythm. The precordial thump is not advocated for unwitnessed cardiac arrest. It may occasionally be useful in witnessed, monitored cardiac arrest showing VF and pulseless VT if a defibrillator is not immediately available. It should not delay prompt chest compressions.

DEFIBRILLATION

The prompt delivery of transthoracic electric shocks is critical to survival in patients with cardiac arrest due to VF or pulseless VT. The earlier these rescue shocks are given the more likely are they to be effective. In fact, rescue shocks are highly effective when VF is of brief duration (1–2 minutes). The chance of successful defibrillation diminishes rapidly over time.[24] The probability of successful defibrillation declines by about 2–10% per minute starting with an estimated probability of 70–80% at time zero.[25] Thus, if a patient with VF is not shocked (defibrillated) within 10 minutes of the onset of collapse or arrest the probability of survival approaches zero.

Interestingly, resuscitation is more difficult and less likely if rescue shocks covert VF into asystole instead of converting VF into a stable organized rhythm. It is also to be noted that pulseless VT or VF may be resistant to cardioversion in the presence of severe hypoxia, acidosis or electrolyte imbalance.

Transthoracic electric shocks act by depolarizing the heart, thereby abolishing the VF wave fronts, and allowing the restitution of a stable cardiac rhythm. In all probability, a critical mass of the myocardium must be depolarized to produce this depolarizing effect. VF may however recur perhaps related to persistent foci within the myocardium which are not depolarized or perhaps because of heterogeneous areas of refractoriness within the heart muscle.[26]

CPR before Defibrillation

The rate of survival is noted to be higher among patients who have experienced an unwitnessed sudden cardiac arrest, if these patients have received CPR for 1.5–3 minutes followed by defibrillation.[27] In a witnessed sudden cardiac arrest, immediate defibrillation is crucial, the patient receiving chest compressions while the defibrillator is being prepared. Chest compressions prior to defibrillation perhaps improve the myocardial readiness for a successful cardioversion by promoting coronary artery perfusion and the supply of oxygen and other metabolic substrates to the myocardium.[16]

Method of Defibrillation

As soon as a defibrillator is available it is attached to the patient and if pulseless VT or VF is present, defibrillation is carried out with a shock of 200 joules. The shock is delivered through paddles (coated with a jelly), one paddle being held firmly in contact with the sternum and the other placed over the left side of the chest in the midaxillary line. The following points are of importance as they add to the likelihood of successful CPR—

- Most available defibrillators now deliver biphasic wave forms as these produce more effective depolarization and achieve defibrillation with less energy than monophasic wave forms.
- The paddles must exert a firm pressure (0.5–0.8 kg) over the sites of application on the chest wall; this decreases chest wall impedance, increasing delivery of the current to the myocardium.
- It is crucial that the transition from the chest compressions (which the patient is receiving) to the delivery of the shock is seamless. Therefore, chest compressions should be continued while the defibrillator is charged and compressions stopped only when the shock is just about to be delivered. Reducing the delay between the last compression and the delivery of a single shock has been associated with more successful resuscitation.[28] Following the delivery of the shock, chest compressions should promptly recommence, the transition from shock back to chest compressions again being seamless.

Prior to 2010, it was recommended that defibrillator shocks were delivered in stacks (2–3 at a time). The current recommendation is to deliver a single shock followed by immediate resumption of chest compressions. This recommendation leads to a minimum interruption of chest compressions, so crucial to successful resuscitation.

Rescue shocks may need to be repeated with multiphasic wave forms but they should be delivered singly in patients with recurrent VF or pulseless VT, with as short an interruption of chest compressions as possible.

- *Hands-on defibrillation* Uninterrupted chest compressions are crucial for recovery of spontaneous circulation. In most units (including ours), chest compressions are necessarily interrupted, though briefly (hands off) during the delivery of the rescue shock. This was due to the fear of electrocuting the rescuer. Recent studies have however shown that it is perfectly safe to continue compressions during the delivery of a defibrillatory shock when a biphasic defibrillator is used with self-adhesive electrodes, and the rescuer wears standard examination gloves.[19] The AHA has not adopted this practice in the 2010 guidelines, but it is likely that in the future, interruption of chest compressions may be recommended only and solely for the purpose of rhythm analysis.

- Current research has shown that quantitative analysis of VF wave forms can distinguish early VF from late VF.[29] Large amplitude wave forms suggest early VF and is associated with greater success in defibrillation. Recording conditions and body build may however affect the amplitude of wave forms. Future generations of defibrillators almost certainly will incorporate devices that provide a real-time semiquantitative analysis as to the probability of a successful cardioversion after delivery of a rescue shock. The intensivist would then use the information to shock VF if the probability of success is high or continue with chest compressions when the probability of success is low.

Pulse Check after Defibrillation[30]

Chest compressions should be resumed immediately after defibrillation. The pulse should not be checked after defibrillation. This is because even if the patient is successfully cardioverted, the myocardium is generally stunned and unable to generate adequate perfusion pressure. The pulse rate and rhythms can be checked at the next 2 minute interval, either at the time when the rescuer is changed, or when the next defibrillatory shock is ready to be delivered. The importance of uninterrupted cardiac compressions lies at the heart of the above recommendation.

If the patient lapses into repeated VF, many defibrillating shocks may need to be given, notwithstanding the fact that repeated shocks may directly damage the myocardium. We have had patients lapsing into repeated VF necessitating numerous defibrillatory shocks. In some of these patients the underlying cause turned out to be a blocked left anterior descending artery (LAD). Coronary angiography with angioplastic stenting of the LAD led to survival.

BASIC AIRWAY MANAGEMENT AND VENTILATION

The current AHA basic life support and the ACLS guidelines place circulation before airway and breathing in patients who experience sudden cardiac arrest from a cardiac cause. This is because in the early stages, patients with sudden cardiac arrest suffer from severe hypoxia to the heart and brain due to decreased or absent perfusion and not due to decreased ventilation. In the above situation oxygen reserves remain adequate for the first few minutes so that giving precedence to ventilation over circulation as was done prior to 2010, reduces the chance of survival. However, in patients who have suffered cardiac arrest from a primary pulmonary cause (drowning, severe respiratory failure, sudden obstruction to the upper airways) a patent airway and ventilation should be restored as quickly as possible. If there are two rescuers at work, this is easily possible as one attends to chest compressions and the other to the airway and ventilation. If there is just one rescuer, the task may prove difficult.

Though attention to circulation precedes that given to the airway and ventilation, it needs to be stressed that CPR cannot succeed if the airway is left obstructed and if ventilation is left unattended. This prevents oxygenation, causing or perpetuating cardiorespiratory arrest.

Obstruction of the airway can occur in any patient who is comatose, including a patient who suffers cardiac arrest from a primary cardiac cause. The airway can be opened by the simple maneuver of extension of the neck (head tilt) and forward displacement of the mandible (chin lift). Following this, positive pressure ventilation can be provided by mouth-to-mouth or bag-mask ventilation. A positive pressure breath of 400 mL delivered in 2–3 seconds is enough to cause a sufficient expansion of the chest. Hyperventilation and hyperexpansion of the chest can do more harm than good as this can impair venous return and decrease circulation during resuscitation. The optimal rate and timing of pressure breaths must be balanced against the fact that interrupting chest compressions frequently leads to a lesser survival rate. As mentioned earlier the ratio of 30 chest compressions to 2 breaths for ventilation has been recommended in the current guidelines.

The view that chest compressions alone without any artificial ventilation may be sufficient to accomplish resuscitation has been mentioned earlier. This view is debatable and is not acceptable to most intensivists.

Relevant AHA recommendations with regard to airway and ventilation are briefly mentioned below.

- The use of 100% oxygen is recommended during initial resuscitation as there is no evidence that it causes harm during short-term resuscitation.
- Chest compressions cause air to be expelled during compression and drawn into the lungs passively during the recoil. Therefore if the airway is patent, the passive inhalation of oxygen via a face mask suffices for several minutes after sudden cardiac arrest.
- Bag-mask ventilation can maintain adequate ventilation. It needs to be performed correctly and preferably needs two trained care-givers. One holds the mask firmly in place from the bridge of the nose on top to well below the mouth at the lower end, so that there is no leak of air or oxygen that is delivered. The other care-giver presses the bag providing a tidal volume of 600 mL over 1 second at the rate of 8–10 breaths per minutes.

An important complication of bag-mask ventilation is insufflation of the stomach. Normally the esophageal tone prevents air entering the stomach unless the upper airway pressure is close to 20 cm H_2O. However, in cardiac arrest, the esophageal muscle tone is decreased allowing insufflation of the stomach with air at an upper airways pressure of 5–8 cm H_2O. Overvigorous squeezing of the bag during the bag-mask ventilation can therefore prove dangerous. Gastric dilatation can cause vomiting, aspiration of gastric contents; it can also impair venous return and decrease lung compliance.

Advanced Airway Management and Ventilation

- Insertion or placement of an advanced airway (such as an endotracheal tube) should be avoided in the initial

phase of resuscitation as the procedure interrupts chest compressions. The procedure should be delayed until the patient fails to respond to initial CPR or defibrillation attempts, or inserted if necessary after there is a successful ROSC. In patients whose circulation has been restored, the presence of coma or respiratory failure is an indication for endotracheal intubation. Endotracheal intubation unquestionably secures a definite airway, but it often involves fairly long interruption in chest compressions even when performed by an expert. Alternative supraglottic airways such as the double-lumen tracheal-esophgeal tubes or laryngeal mask airways can therefore be used to temporarily control the airway during resuscitation. These devices can be inserted blindly in seconds without laryngoscopy and without interrupting the chest compressions. Intensivists therefore often use supraglottic airways as the first advanced airway during resuscitation. After endotracheal intubation, the patient is given ventilator support.

- Continuous wave form capnography together with clinical assessment is the best way to assess correct placement of an endotracheal tube. Capnography also helps to judge ROSC. A rise in the $EtCO_2$ by more than 10 mm Hg often heralds recovery of circulation and gives hope for a successful resuscitation.
- If the patient is ultimately on ventilator support, he or she should be provided 8–10 breaths per seconds. Higher ventilation rates and large tidal volumes (as has been mentioned earlier) increase intrathoracic pressure resulting in diminished venous return and a reduced cardiac output.

MONITORING CARDIOPULMONARY RESUSCITATION

The two most important parameters that need to be monitored are the continuous ECG recordings (through electrodes placed on the three limb leads and connected to an ECG monitor) and the presence of pulses.

ECG Callaway CW[31] gives an excellent practical division of ECG rhythms into organized and non-organized. Organized rhythms include supraventricular rhythms and VT. Non-organized rhythms include VF and asystole. Non-organized rhythms cannot support the pumping of the heart and therefore cannot support circulation. Callaway rightly points out that restoring cardiac electrical activity to an organized and stable rhythm is essential for successful resuscitation. Organized rhythms can support circulation unless the rate is too slow less than 30/minute or too fast greater than 180/minute. An organized rhythm in the absence of pulses is termed pulseless electrical activity (PEA), formerly termed electromechanical dissociation. The absence of perfusion and of pulses in the presence of an organized rhythm is due to severe damage to the heart muscle [as in massive myocardial infarction (MI)] or following cardiac rupture or following uncoupling of electrical and mechanical activity (as in prolonged circulatory arrest). Other important causes of PEA are massive pulmonary embolism, tension pneumothorax and cardiac tamponade.

Perfusion may not be absent but yet be very poor in pulseless VT, supraventricular tachycardia (SVT) and atrial fibrillation with a very rapid ventricular response. These rhythm disturbances though organized need prompt correction through rescue shock to improve the circulatory state.

In patients with a PEA, the rate of complexes in the ECG may be used to monitor resuscitation efforts. With increasing myocardial ischemia due to a fall in coronary perfusion, the rate of PEA will slow. If resuscitation is leading to improved coronary perfusion and improved supply of nutrients to the heart, the rate of PEA will steadily increase. Often narrow ECG complexes exceeding 80/minute herald return of pulses and successful resuscitation. Falling rates of ECG complexes in PEA signal failure to resuscitate.

The ECG monitor can also demonstrate the presence of asystole or VF. Reperfusion of the heart in asystole (through chest compressions and ventilation) may restore VF. Also an increase in the amplitude of fibrillating waves in VF points to improved coronary reperfusion. On the other hand, a deterioration of VF to asystole is observed when resuscitation attempts are unsuccessful.

Pulses The presence of a palpable pulse denotes mechanical activity of the heart and when combined with an organized stable rhythm as seen on the ECG monitor denotes successful resuscitation. The importance of not interrupting chest compressions to feel the pulse has already been stressed.

It should be noted that a satisfactory arterial pressure or a palpable peripheral pulse during chest compressions does not necessarily reflect coronary perfusion pressure because ventricular pressures are elevated simultaneously as well. Therefore, palpable pulses during chest compressions (through a necessary accompaniment to chest compressions) may be misleading. The clinician should look for other evidence of improved coronary perfusion—as for example a return of the ECG to an organized stable rhythm, a palpable pulse during a break in the chest compressions and a rise in the $EtCO_2$.

Oximetry Monitoring O_2 saturation through oximetry is useful to determine the presence or absence of hypoxemia during resuscitation.

Capnography It allows the intensivist to monitor the $EtCO_2$. A rise in $EtCO_2$ by 10 mm Hg often heralds a possible ROSC.

Arterial pH and, PaO_2 and $PaCO_2$ need to be monitored so as to allow if necessary any correction of metabolic or respiratory acidosis.

Serum electrolytes This again may well be important as hypokalemia, hyperkalemia; hypomagnesemia may well be responsible for arrhythmias or even arrest and need to be corrected for successful resuscitation.

Any other investigation which is necessary to determine the possible cause of cardiorespiratory collapse needs to be done as it is important to remove or counter the cause if successful resuscitation is to be achieved.

PHARMACOLOGICAL THERAPY

Drugs chiefly used in cardiac arrest are vasopressors, inotropes, and antiarrhythmic drugs. Sodium bicarbonate may need to be administered to patients who develop well marked metabolic acidosis. Electrolyte disturbances may need appropriate correction, particularly with regard to potassium, magnesium and calcium.

Vasopressors

There is evidence to show that vasopressors improve circulation during CPR. They act by raising systemic arterial pressure, increase coronary perfusion pressure so that restoration of pulses is more likely. Though current data in patients with out-of-hospital cardiac arrest concludes that no drug therapy influences long-term survival, vasopressors must nevertheless always be used. The two vasopressors in common use are epinephrine and vasopressin. Epinephrine increases coronary perfusion pressure and systemic arterial pressure through stimulation of α-adrenergic receptors. Epinephrine is administered intravenously in 1 mg increments (0.015 mg/kg). The duration of the action of epinephrine in cardiac arrest is brief lasting just a few minutes, so the dose needs to be repeated. Also the dose of 1 mg is perhaps too small to produce a significant effect on the circulation. The dose should therefore be stepped up and in most patients needs to be used at frequent 3–5 minute intervals.[8] A 15 mg dose compared to 1 mg in patients with out-of-hospital arrests showed a significantly higher rate of restoration of the pulses and admission to hospital in those receiving the larger dose.[32] Yet, the overall survival rate was the same in both groups. A dose of 7 mg when compared to 1 mg showed no difference either in restoration of pulses or in survival, both in patients with in-hospital and out-of-hospital arrests.[33] Though no definite dosage can be recommended, the drug is best used in progressive increments at 3–5 minute intervals in the hope of restoring circulation and palpable pulses.

Vasopressin acts on the vasopressin receptors raising the blood pressure and coronary perfusion pressure helping thereby to restore the pulses. It is administered IV as 40 unit boluses (0.5 mg/kg). Its action is longer lasting (10 minutes) than epinephrine, so it may be repeated if necessary at 10 minutes intervals. Both epinephrine and vasopressin are titrated with reference to the ECG wave forms, presence of pulses and changes in $EtCO_2$. There is no evidence to show that any one of these vasopressor is superior to the other. Nor does combination of these vasopressors confer added benefit.[34]

Inotropes

The inotrope most commonly used is dopamine, particularly in patients with a past history of IHD or in patients whose cardiac arrest is directly related to an acute myocardial infarction (AMI).

It must be stated that though clinical data and experience support an increased probability of restoring spontaneous circulation following the use of vasopressors during CPR, there is no clear evidence that their use, improves overall survival.

Antiarrhythmic Drugs

A vagally induced bradyarrhythmia may be corrected by IV atropine. However, the nervous system does not influence the heart rate once circulatory arrest has been present for 2–3 minutes. Once VF is established the only drug of use is amiodarone (5 mg/kg given as bolus). The drug works even better on pulseless VT. If a stable organized rhythm is restored after its use in VF or pulseless VT, the drug should be given prophylactically in an IV infusion (750–1000 mg) over 24 hours. Unquestionably the therapy of choice for VF or pulseless VT is a rescue shock. If, however, VF or pulseless VT persists after three rescue shocks, amiodarone should be given a try.

In earlier years, lidocaine, procainamide, and bretylium have been used for VF. These drugs have no effect once VF has occurred, though they may suppress the arrhythmia before its occurrence. Even as prophylaxis, amiodarone has replaced each one of these drugs. Occasionally, we have successfully used both amiodarone and lidocaine in separate infusions as prophylaxis for recurrent VT not controlled by either one or the other of these drugs.

All pharmacotherapy is given intravenously. It is however important to bear in mind that if the endotracheal tube is in place but if for some reason an IV line has not been secured, a few emergency drugs can be effectively administered via the tube. Medications given by this route should be given in a dose 2.5 times that recommended for IV use, and should first be diluted in 10 mL normal saline or distilled water. The emergency drugs which are thus absorbed and are effective after administration through the endotracheal tube are epinephrine, lidocaine and atropine.

Treatment of Metabolic Disturbances

Intravenous Bicarbonate is used to improve metabolic acidosis (pH <7.2). Cardiac function is believed to improve once metabolic acidosis has been corrected. Though the use of bicarbonate in the presence of acidosis has shown higher rates of successful resuscitation, there is as yet no evidence to show an improved outcome.

Hypokalemia and hyperkalemia are important trigger factors for VT, VF. Hyperkalemia can cause a sudden bradyarrhythmia, wide ventricular complexes with absent P waves. Marked ST changes may also be present. Pulseless electrical activity may supervene. This precipitating factor should always be kept in mind, particularly in patients with chronic renal failure who are on angiotensin-converting-enzyme (ACE) inhibitors. Correction of hyperkalemia in addition to the usual CPR procedures often leads to survival with good ultimate outcomes.

Similarly marked abnormalities in calcium, magnesium need correction as they may contribute to cardiac arrest.

Stopping Efforts to Resuscitate

Mere survival in a vegetative state can be an unfortunate sequel of CPR. The risk of organ dysfunction or failure in particular brain damage is related directly to the duration of ischemic insult. The ischemic time following an arrest includes the time from the onset of arrest to the start of CPR (arrest time) plus the duration of CPR efforts. In the study by the Brain Resuscitation Clinical Trial I Study group, Abramson et al. found that if the arrest time is less than 6 minutes and the CPR time does not exceed 30 minutes, half of the survivors had a good neurological recovery. If, however, the arrest time exceeds 6 minutes, a CPR lasting more than 15 minutes always resulted in a significant neurological impairment in the survivors. Though it is perhaps impossible to be dogmatic, this observation suggests that CPR should be continued for at least 30 minutes if the arrest time is less than 6 minutes. If the arrest time is longer than 6 minutes, the CPR should be terminated after 15 minutes.[35]

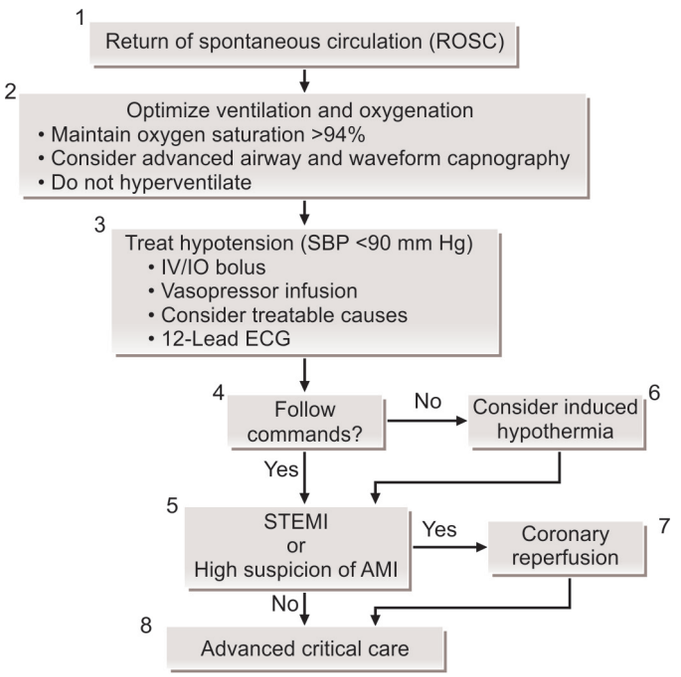
POST-CARDIAC ARREST MANAGEMENT

Good post-cardiac arrest intensive care after successful resuscitation is crucial for a good ultimate outcome (Flowchart 2). The single most important objective to bear in mind at this stage is the prevention of brain injury. Though brain ischemia and injury can occur during prolonged CPR, most of it develops as an active process over hours to days after resuscitation. In other words, it is a reperfusion injury.

Several cellular and molecular mechanisms contribute to brain injury.[36] During brain ischemia and soon after reperfusion there is an increased release of stimulatory amino acids, free radicals that harm both neuronal integrity and function. There are focal disturbances in blood flow and an inhibition of protein synthesis.[37] The activation of several extracellular and intracellular signaling pathways leads to specific changes in gene transcription.[38] Most importantly after 24–72 hours of reperfusion there is an activation of specific proteases which lead to neuronal death. Brain injury with neuronal death probably results as a culmination of all these metabolic changes observed after reperfusion is established. There is no drug as yet that has been shown to prevent or counter brain injury. Calcium channel blockers, magnesium, diazepam, thiopental have been tried in randomized trials but without benefit. This is because there are multiple mechanisms contributing to neuronal injury and death, and a single drug is not likely to act on all of these mechanisms. Perhaps different classes of drugs, each acting on different mechanisms causing brain damage may in the future be discovered. Today, the focus on post-cardiac arrest intensive care rests on—

- Achieving therapeutic hypothermia (32–34°C) for 12–24 hours after resuscitation.
- Maintenance of a cardiocerebral perfusion pressure.
- Early cardiac catheterization with a view to opening up and stenting critically blocked coronary vessels if these be present.

Flowchart 2: Adult immediate post-cardiac arrest care



Source: Adapted with permission from Adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 122.

Abbreviations: ECG, electrocardiography; IO, intraosseous; IV, intravenous; STEMI, ST segment elevation myocardial infarction; AMI, acute myocardial infarction

Management of Post-resuscitation Arrhythmias

After resuscitation, patients may develop arrhythmias. Atrial tachycardia is often met with. Flowchart 3 given below outlines briefly their management.

The management of postresuscitation bradyarrhythmias is given in Flowchart 4.

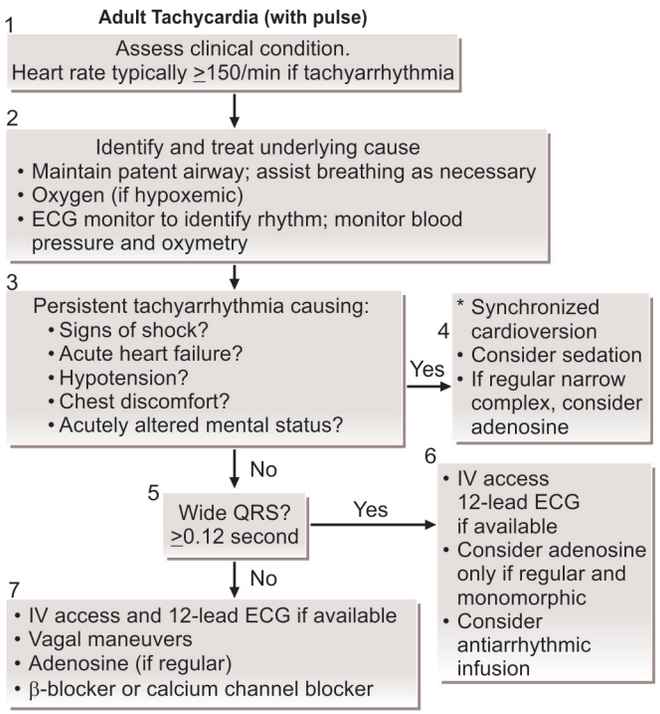
Also, refer to treatment of cardiac arrhythmias in the Section Cardiovascular Problems Requiring Critical Care.

Induced Hypothermia

Induction of mild hypothermia (32–34°C) for 12–24 hours after resuscitation produces a 24–30% relative risk reduction for death or poor neurological outcome.[39] Survival and neurological outcomes were favorable when hypothermia was used in patients resuscitated from VF or cardiac arrest. It is advocated that hypothermia should be used in all patients who remain comatose after resuscitation from a cardiac arrest whatever the initial rhythm. To be maximally effective cooling should be achieved within 6 hours after resuscitation and should be continued from 12 to 24 hours; rewarming should then be performed slowly (< 0.25°C/hour).

Hypothermia can be induced by either surface cooling or through endovascular devices. Surface cooling is achieved by ice packs and cooling blankets. Neuromuscular blockade

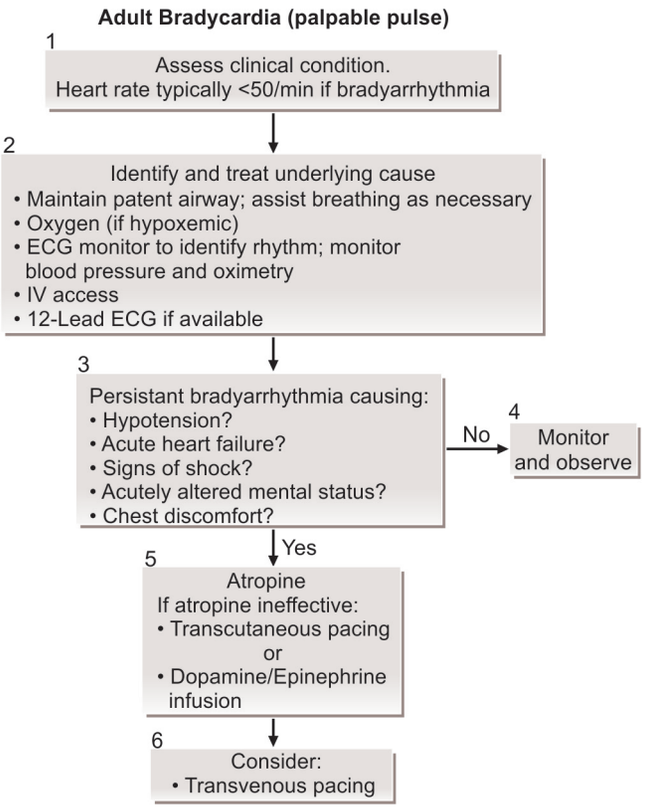
Flowchart 3: Management of atrial tachycardia



* For narrow regular tachycardia: 50–100 J
Narrow regular: 120–200 J biphasic or 200 J monophasic
wide regular: 100 J

Source: Adapted with permission from Adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 122.

Flowchart 4: Management of post-resuscitation bradycardia in adults



Source: Adapted with permission from Adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 122.

and sedation may help if shivering or other compensatory responses interfere with surface cooling.

Endovascular cooling through endovascular catheters perhaps allows more stable control over time. An efficient quick method of cooling is the bolus infusion of cold (4°C) IV crystalloid solution 30 mL/kg (unless contraindicated). Hypothermia can then be maintained by either surface cooling or endovascular cooling. Use of sedation and at times neuromuscular blockade enhance the cooling effect. There is a high incidence of seizures after cardiac arrest, hence neurophysiological monitoring should be in place if neuroparalytic agents have been used.

Hypothermia can lead to an increased incidence of infections if prolonged over 24 hours. Mild hypothermia can inhibit platelet function and coagulation but bleeding complications are rare. Elevation of pancreatic enzymes and a fall in creatinine clearance may be observed during cooling. All these disorders are corrected following rewarming.

Two important points in neurological care of the post-cardiac arrest patients is (1) to prevent any fever over the first 24–48 hours of brain injury; (2) monitor for seizures if an electroencephalogram (EEG) is available.

Maintenance of Cardiovascular Perfusion Pressure

After resuscitation from cardiac arrest, myocardial function is impaired. Hence, a degree of both vasopressor and inotropic support becomes necessary in patients where the resuscitation time has been 3–4 minutes or more. Dependence on support usually diminishes over 24–72 hours.

Following successful resuscitation, there is evidence to show that within the first 24 hours there is increased cerebral vascular resistance and impaired cerebral autoregulation.[40] Available data suggests that relative hypertension, with a mean arterial pressure of 80–100 mm Hg should be maintained, provided the heart can tolerate the increase in afterload. It has been noted that hypotension soon after resuscitation is associated with increased neurological damage in patients admitted to the hospital after cardiac arrest. Dopamine 5–20 μg/kg per minute and norepinephrine (0.01 μg/kg per minute) are often used to increase blood pressure and maintain an effective coronary cerebral perfusion.

Early Cardiac Catheterization

Every patient resuscitated from cardiac arrest is a candidate for cardiac catheterization with a view to opening and stenting

Box 1: Main focus in post-cardiac arrest care

- Hypothermia (32–34°C) for 12–24 hours—
  - Slow rewarming
  - Counter seizures; avoid and counter fever particularly in first 48 hours
- Maintain coronary cerebral perfusion—
  - Mean arterial pressure 80–100 mm Hg through use of dopamine, norepinephrine
- Consider early cardiac catheterization in patients with IHD

Abbreviation: IHD, ischemic heart disease.

one or more blocked coronary arteries. Most cardiac arrests are due to underlying IHD; hence most patients would require the above approach. Primary angioplasty can be conducted in patients undergoing hypothermia treatment. The presence of continuing coma is no contraindication to primary angioplasty.

Glucose Control

Elevated blood sugar levels are associated with poor outcome after cardiac arrest.[41] Available data suggests that the blood sugar should be maintained within 140–180 mg/dL. Stringent blood sugar control (72–108 mg/dL) is controversial and may do more harm than good.

Use of Anticoagulants

Cardiac arrest is characterized by an activated coagulation profile and diminished fibrinolysis. The profile resembles a mild form of disseminated intravascular coagulopathy, which may contribute to multiorgan dysfunction. The use of low molecular weight heparin has been advised by some workers to counter the above hematological change.

Finally meticulous intensive care needs to be given to all other organ systems, to correction of fluid, electrolyte disturbances and to prevention and treatment of possible nosocomial infections.

Salient features of intensive care following post-cardiac arrest resuscitation are briefly tabled below (Box 1 and Table 1).

Neurological Sequelae

In spite of expert management even in good centers, neurological sequelae are all too common—

- *Brain death* This is the most catastrophic sequel. Brain death has been accepted by an Act of Parliament, as the criterion for death, even in the presence of continuing heart action or beat.

Brain death is characterized by an unarousable state of coma, a flat EEG, and absent brainstem reflexes. These include absent doll's eye movements, no eye movements on stimulation of the labyrinth by cold water syringed into the auditory canal, and absent corneal, pupillary, gag and cough reflexes. There is also absence of spontaneous breathing. The apnea test is considered positive if there is no evidence of spontaneous ventilatory efforts for at least 3 minutes, and the $PaCO_2$ is greater than 60 mm Hg at the end of the test.

Table 1: Important features in the care of organ systems in post-cardiac arrest

CVS	• Counter arrhythmias • Amiodarone prophylaxis • Mean arterial BP 80–100 for the first 24–48 hours • Primary angioplasty in inpatients with MI or IHD
RS	• Avoid hypoxia • Avoid hyperventilation • Prevent and treat nosocomial infections
GI	• Consider early refeeding after hypothermia to prevent translocation of bacteria
CNS	• Hypothermia, CT to exclude an intracranial bleed or detect a massive recent infarct • Monitor (EEG) and counter seizures • Sedation + muscle relaxant if needed for hypothermia • Periodic CNS examination • MRI, EEG to help with prognosis
Infection	• Prevention and treatment of nosocomial infections
Metabolism	• Correction of fluid and electrolytes imbalance • Correction of acidosis with sodium bicarbonate

Abbreviations: CVS, cardiovascular system; MI, myocardial infarction; IHD, ischemic heart disease; RS, respiratory system; GI, gastrointestinal; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram.

The local spinal reflexes may be preserved in a brain-dead individual. Deep tendon reflexes may thus continue to be elicitable. The heart and circulation can function effectively for as long as 2 weeks or even longer if ventilatory support is continued. Before the Act of Parliament, which legalized brain death as amounting to death (even if the heart continues to beat), there used to be tremendous pressure from concerned and at times angry relatives to continue with life support even though the futility and anguish of this was adequately explained. Prior to the legislation of brain death as death, the longest survival we have recorded after brain death has been close to 3 weeks. Gradually, multiple organ failure sets in. An interesting feature is the occurrence of diabetes insipidus perhaps due to involvement or injury to the hypothalamus and pituitary. Another noteworthy feature is the frequent occurrence of hyperglycemia in these patients. Failure of gastrointestinal (GI) function is characterized by absent peristalsis, yet without any associated distension. Perhaps there is a decrease and virtual cessation of secretion of digestive and other fluids within the GI tract. Invariably there is a final and merciful fall in the blood pressure, or the development of a malignant arrhythmia, which pulls the curtain on the tragic scene.

- *Alteration in the state of consciousness* It is a frequent sequel of CPR. This alteration may take the form of coma, a vegetative state, a locked-in state, or stupor. Coma is an unconscious state with absence of verbal communication, inability to respond to or to localize noxious stimuli,

and an absence of spontaneous opening of the eyes. A vegetative state is similar to coma except that the patient opens his eyes spontaneously, and may appear to look around. A locked-in state is due to a brainstem lesion in which though there is no movement of the limbs, the patient is aware of his surroundings; he cannot speak but can communicate with his eyes. Stupor is a comparatively benign sequel in which the patient is arousable by a noxious stimulus; significant and at times complete recovery can ensue from this stage. Mental obtundation and amnesia for present as well as past events are often observed for 24–48 hours after successful resuscitation; here recovery is the rule.

- *Cortical blindness* It is sometimes seen after recovery. This type of blindness is associated with an intact optic nerve and a normal retina. The condition usually improves over a period of time though full recovery may not occur. The longer it persists, the greater the likelihood of permanent impairment of vision.
- *Seizures* These are an important sequel in the first 24 hours. In the worst form, they present as a status epilepticus, which may be impossible to control and which carry a grim prognosis of impending brain death. Epilepsy partialis continuosa is characterized by repetitive clonic movements of a limb. These often disappear as further recovery of the central nervous system (CNS) ensues. Myoclonic jerks are irregular jerky movements, which can be localized or generalized. Myoclonic jerks particularly when generalized, or involving the eyes and facial muscles, carry a grim prognosis and generally forecast impending brain death.

Anticonvulsant therapy as outlined in a later chapter should be given, but more often than not, is ineffective, particularly in status epilepticus or in generalized myoclonus. Seizures uncontrolled by the conventional use of dilantin, or by the use of diazepam or lorazepam in a continuous IV infusion, can at times be controlled by 500–1000 mg of thiopentone, given intravenously as a slow infusion over 24 hours.

PROGNOSIS OF NEUROLOGICAL RECOVERY BASED ON CLINICAL EXAMINATION

- Persistent coma in the first few hours after CPR does not necessarily denote prolonged or permanent neurological damage. However, coma persisting beyond 6–8 hours is associated with a poor prognosis. A study on 500 patients by Levy et al.[42] showed that if coma persisted for 1 day, only 10% of patients showed good neurological recovery. The recovery rate was less than 5% when coma persisted for a week; no patient recovered neurological function when coma persisted over 2 weeks. A Glasgow coma score of less than 5 on the 3rd day of coma is also of ominous prognosis and almost always indicates a poor outcome or a permanent severe neurological deficit.[43]
- Brainstem reflexes (doll's eye movements, response to cold water irrigation of the external auditory canal, pupillary and corneal reflexes) are often absent immediately after successful resuscitation. Their return within 1–2 hours is a good prognostic sign for possible recovery. The absence of pupillary or corneal reflexes at 6–24 hours after arrest carries a grim prognosis. Levy et al.[44] noted that not a single patient with absent pupillary or corneal reflexes 24 hours following CPR, was restored to a good quality of life.

The data given above is useful not only in predicting prognosis, but in identifying patients in whom critical care is likely to prove futile. In the West, care after restoring circulation is invariably stopped if clinical findings (as mentioned above) supplemented at times by EEG and imaging studies point to a hopeless quality of life. In our part of the world, it is often impossible to do so, as very often close relatives insist on continuing care at whatever cost and whatever the anticipated sequel unless one can give proof of the presence of brain death.

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SECTION

3

Basic Cardiorespiratory Physiology in the Intensive Care Unit

- Basic Cardiorespiratory Physiology in the Intensive Care Unit

CHAPTER 5

Basic Cardiorespiratory Physiology in the Intensive Care Unit

INTRODUCTION

All important organs and organ systems in the human body are interrelated and interdependent. This interrelation and interdependence is most marked and evident between the heart and circulation on the one hand, and the lungs on the other. The heart (circulatory system) and the lungs (respiratory system) form a single inseparable unit whose purpose is to supply oxygen to the tissues, and to remove carbon dioxide produced during tissue metabolism.

In any and every critical illness, adequate oxygen delivery or oxygen transport to tissues is crucial for proper function of different organ systems, and for survival. Oxygen delivery is controlled by, and is dependent on the cardiorespiratory system as a whole. Poor function or failure of this system is a common theme in numerous critical illnesses in the intensive care unit (ICU). Cardiorespiratory failure invariably heralds a decline in the clinical state of a critically ill individual. Cardiac failure has repercussions on pulmonary function and gas exchange. Respiratory failure sooner or later worsens cardiac function. A vicious spiral of deteriorating cardiorespiratory function spells death in any critical illness. It is therefore important for the intensivist to be aware of basic cardiopulmonary functions and the factors, which affect these functions, particularly in relation to critical care medicine.

This chapter briefly describes factors regulating cardiac function. It then very briefly outlines basic concepts of gas exchange within the lungs, which relate to the assessment and care of critically ill patients. It then goes on to stress the importance of oxygen content of blood, oxygen transport, and the interrelationship, as illustrated by the Fick principle, between oxygen consumption, oxygen transport, and tissue needs for oxygen.

FACTORS REGULATING CARDIAC OUTPUT

The regulation of the cardiac output (Q_T) is complex, particularly in critically ill individuals, and is dependent on tissue factors, neurohormonal factors, and on intrinsic cardiac mechanisms.

Tissue Factors

The cardiac output is basically governed by the tissue needs for oxygen and nutrients. Each organ has a built-in autoregulation of blood flow through arteriolar dilatation and vasoconstriction. The mechanism of this autoregulation is incompletely understood. It is related to local release of vasodilator substances and other locally operating vasoregulatory mechanisms.

Neurohormonal Influences

Neurohormonal factors also play a crucial role in regulating cardiac output. Increased sympathetic activity is very important for increased cardiac output in stressed states. Neural and hormonal influences mediate compensatory mechanisms in a patient in acute circulatory failure. These neurohormonal compensatory mechanisms are life-saving as they override local autoregulatory tissue mechanisms, reduce flow to the skin, muscles and the splanchnic circulation, and maintain an adequate flow to the brain, heart and other vital organs during shock.

INTRINSIC CARDIAC MECHANISMS

The heart has a significant reserve, which enables it to increase its cardiac output whenever necessary. This reserve may be

impaired or totally absent in patients with cardiac disease. Increase in cardiac output can be brought about by an increase in the heart rate and in the stroke volume. The stroke volume is governed by the following factors—

- Preload or the end-diastolic fiber length, or the end-diastolic ventricular volume (Frank-Starling's law).
- Contractility or the force of myocardial contraction, as determined by inherent contractile properties of the myocardium, and by neurohormonal influences.
- Afterload which is the degree of wall tension developed during ventricular ejection.

Preload

This is the degree of stretch of myocardial fibers at end-diastole, just prior to myocardial contraction. The Frank-Starling law states, the energy of contraction however measured, is a function of the length of the muscle fibers.[1,2] The greater the stretch of muscle fibers within physiological limits, the stronger the force of contraction. The resting length of myocardial fibers is related to end-diastolic ventricular volume. Thus increased venous return increases the stretch of muscle fibers, increases the diastolic volume, and is translated into an increased cardiac output. The heart can therefore vary stroke volume and Q_T in response to changes in venous return and tissue needs. The Frank-Starling mechanism is an intrinsic property of muscle, and is independent of neural and hormonal factors. The normal heart can handle an increase in venous return to 2–3 times normal, even if denervated.[3] When a further increase in Q_T becomes necessary, neurohormonal factors must come into play.

Venous return by its influence on the preload, is one of the most important factors governing cardiac output. Venous return is governed by several factors. An important factor is the difference between the mean systemic pressure and the right atrial pressure. The mean systemic pressure is the volume weighted average pressure in the entire circulation—arteries, capillaries and veins, and is chiefly determined by the total blood volume and the tone of the vessels. It averages about 7 mm Hg. The greater the difference between the mean systemic pressure and the right atrial pressure, the greater the venous return. The relationship between the mean systemic pressure and the right atrial pressure is illustrated in graphic form by Guyton (Fig. 1).[4] An increase in right atrial pressure without a corresponding increase in the mean systemic pressure sharply reduces venous return. Venous return stops when right atrial pressure equals mean systemic pressure. This is exactly the circulatory disturbance underlying cardiac tamponade.

The veins are far more distensible than the arteries, so that a small increase in venous tone results in a large volume of blood being returned to the heart. Similarly, a decrease in venous tone leads to pooling of blood in the peripheries, with a decrease in the volume of blood returned to the heart. Thus, venous pressure constitutes a very large portion of the mean systemic pressure, and is the most important factor in determining venous return. Venous pressure in turn is largely dependent on volume of blood within the veins, and on venous tone.

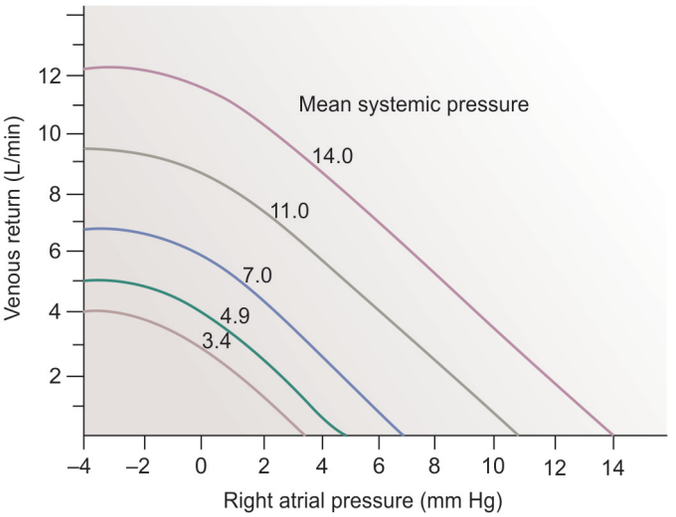


Fig. 1: Effects of mean systemic pressure and right atrial pressure on venous return to the right heart. The greater the difference between the mean systemic pressure and the right atrial pressure, the greater the venous return. Increase in right atrial pressure without a corresponding increase in the mean systemic pressure causes a sharp fall in venous return

Source: Adapted from Guyton AC, Jones CE, Coleman TG. Circulatory Physiology, Cardiac Output, and its Regulation. In: Clemmer TP (Ed). PA: W B Saunders; 1973. Cardiopulmonary Critical Care Management. Elsevier Inc.;1988.

Measurement of Preload and Its Significance in Critical Care Medicine

It is difficult to measure end-diastolic volume in critically ill patients in the ICU. The next best option is to measure end-diastolic pressure or the filling pressure of the ventricle, as an indirect measure of the preload. The higher the filling pressure within physiological limits, the greater the preload and the greater the force of ventricular contraction. The upper normal limit of the left ventricular end-diastolic pressure is 15–17 mm Hg. Cardiac output can be augmented in critically ill patients by increasing the left ventricular filling pressure to an optimum of 15–17 mm Hg, and in some instances to even 20 mm Hg. A further increase in the filling pressure will not increase cardiac output, but will lead to an increase in backward pressure and pulmonary edema. In a critically ill patient, a high left ventricular filling pressure (measured clinically as the pulmonary capillary wedge pressure) is usually related either to myocardial dysfunction, or to fluid overload.

Can one equate left ventricular end-diastolic pressure (LVEDP) to left ventricular end-diastolic volume (LVEDV)? The relation between LVEDP and LVEDV is dependent on the following—

- The venous return and volume of blood distending the left ventricle at end-diastole.
- The compliance or degree of stiffness or distensibility of the ventricle.

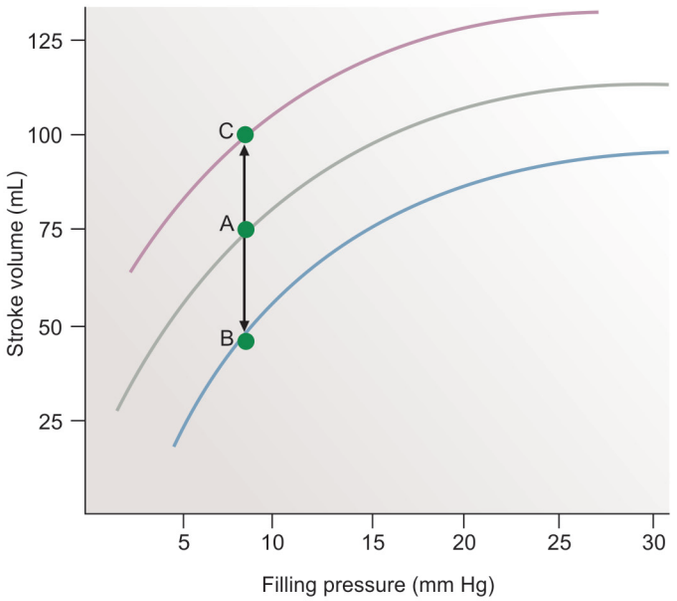
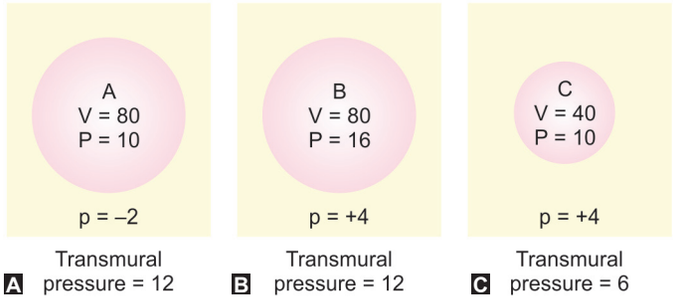


Fig. 2: Ventricular function curve showing effect of ventricular compliance on stroke volume and end-diastolic filling pressures. It should be noted that a reduction in ventricular compliance causes a fall in the stroke volume (A→B), without any change in the filling pressure. Similarly, an increase in ventricular compliance results in an increased stroke volume (A→C) for the same filling pressure



Figs 3A to C: Influence of transmural pressure on pressure-volume relationships in the ventricle. In B, as compared to A, the intrapleural pressure (p) has risen from -2 to +4 mm Hg, and the intraventricular pressure (P) has increased to the same extent (from 10 to 16 mm Hg). The transmural pressure gradient remains the same, and therefore the intraventricular volume (V) is unchanged. If however, as in C, the rise in intrapleural pressure (pressure surrounding the heart) is not associated with a corresponding rise in intraventricular pressure, the transmural pressure gradient is reduced, and the intraventricular volume falls
Source: Modified from Clemmer TP (1988), as in Fig. 1

- The transmural pressure, i.e. the pressure surrounding the ventricle.
- The volume of the right ventricle, which shares a common wall (the septum) with the left ventricle, and a common limiting pericardial sac.

Venous pressure and its relation to venous return has already been briefly discussed earlier. It is a major factor influencing both ventricular end-diastolic filling pressure and end-diastolic volume.

Compliance of the Ventricle Altered compliance or distensibility is also important in determining fiber length. Compliance can be regarded as the change in end-diastolic volume (ΔEDV) in relation to change in end-diastolic pressure (ΔEDP).

$$\text{Compliance} = \Delta EDV/\Delta EDP$$

A fall in compliance (i.e. a decrease in diastolic distensibility), will lead to a rise in end-diastolic pressure for any given diastolic volume. If a ventricular function curve of stroke volume against end-diastolic filling pressure is plotted, the stroke volume will fall for the same filling pressure, if the compliance is reduced. When ventricular compliance is markedly reduced (stiff, very poor distensibility), two effects follow: (1) the stroke volume is sharply reduced because the ventricular end-diastolic volume is reduced; (2) the high left ventricular end-diastolic pressure needed to distend the stiff ventricle leads to pulmonary congestion and edema. The decrease in stroke output that accompanies a decrease in ventricular compliance is termed diastolic dysfunction or diastolic heart failure, as it is independent of any change in the systolic function (i.e. contractility) of the ventricle. In clinical medicine, it is important that a fall in stroke volume due to decreased compliance (poor distensibility) is not wrongly attributed to a reduction in contractility.

In a similar fashion, a decrease in ventricular compliance would lead to an increase in end-diastolic volume, and to an increased stroke volume for the same filling pressure (Fig. 2).

Ventricular compliance does alter in critical illnesses. Compliance is reduced for example, in ischemia to the ventricle, in hemorrhagic and septic shock, and following the use of inotropic drugs like dopamine, epinephrine, and isoproterenol.[5] Compliance on the other hand is increased after relief of ischemia, in cardiac dilatation, and after drugs such as nitroglycerin and nitroprusside.[6-8]

Transmural Pressure Transmural pressure also influences the pressure-volume relationships in the ventricle. This is illustrated in Figures 3A to C. The intrapleural pressure has risen from –2 to +4 mm Hg; the intraventricular pressure (P) has increased to the same extent (from 10 to 16 mm Hg). The transmural pressure gradient remains the same, and therefore the intraventricular volume (v) is unchanged. If however; the rise in intrapleural pressure (pressure surrounding the heart) is not associated with a corresponding rise in intraventricular pressure, the transmural pressure gradient is reduced, and the intraventricular pressure falls. The measured stroke volume is thus the same with a higher LVEDP. This could be wrongly interpreted as a fall in contractility, or to a decreased compliance, when in point of fact it is related to an increase in the intrapericardial or intrapleural pressure. The former can result from pericardial effusion, and the latter may occur in patients on ventilatory support, particularly when positive end-expiratory pressure (PEEP) is being used.

Volume of the Right Ventricle Acute dilatation of the right ventricle can shift the interventricular septum towards the left ventricular cavity, reducing left ventricular end-diastolic volume without any apparent change in left ventricular end-diastolic pressure. This has been observed to occur following a sharp increase in pulmonary vascular resistance due to pulmonary embolism, in acute respiratory failure, and with use of high levels of PEEP. Acute right ventricular dilatation may thus reduce left ventricular filling and cardiac output.

In summary, the left ventricular filling pressure (the pulmonary capillary wedge pressure as measured through a Swan-Ganz catheter) is a good index of the preload. However, when interpreting pressure readings, or when manipulating filling pressures through volume infusions, the influence of the compliance of the ventricle, as also of the intrapleural and intrapericardial pressures should be given due consideration. Septal shifts due to acute right ventricular dilatation may also compromise left ventricular end-diastolic volume, and interfere with left ventricular filling, for reasons stated above.

Contractility

Stroke volume can be increased not only by augmenting preload, but also by increasing contractility. This is accomplished by the use of inotropes that increase both isometric force, and the velocity of isotonic muscle shortening at all loads. Neurohormonal mechanisms within the body, by stimulating beta-1 agonist receptors in the ventricles, also increase contractility with improved emptying of the ventricles, for any given diastolic length.

Afterload

This is an important factor governing stroke volume. Afterload is the ventricular wall tension generated during systolic ejection of blood from the ventricles. The aortic pressure is an important determinant of left ventricular afterload. Increasing the afterload moderately in a normal heart, causes a slight fall in the ejection fraction. This results in a compensatory increase in fiber length and diastolic volume, with stronger contraction and an improved ejection fraction. On the other hand, an increased afterload in a diseased heart, which has poor contractility, can be disastrous. It results in a profound fall in the ejection fraction, and in the forward flow from the heart.

The relationship of a changing afterload to a failing heart is more clearly illustrated by the application of Laplace's law,

$$T = \frac{Pr}{2h}$$

where T is the wall tension (afterload). T is not only directly related to the intracavitary pressure (P), but also directly related to the radius of the chamber (r), and inversely to (h), the thickness of the ventricular wall. Thus, T (wall tension or afterload) increases with the increased radius of a dilated heart. It is reduced with hypertrophy or increased thickness of the ventricular wall.

Influence of Pleural Pressure on Afterload

Negative intrapleural pressures increase transmural pressure and increase ventricular afterload. Negative pressure surrounding the heart acts by impeding the inward movement of the ventricular wall during systole.[9] This is responsible for a reduced cardiac output and reduced systolic blood pressure during the inspiratory phase of spontaneous breathing. When the fall in inspiratory-related pressure during systole is greater than 15 mm Hg, it is termed pulsus paradoxus. There is nothing paradoxical about this observation, as it is merely an exaggeration of a normal response.

Positive intrapleural pressure can reduce the afterload, by promoting the inward movement of the ventricular wall during systole, thereby facilitating ventricular emptying. It is likely that the beneficial effects of closed chest compressions performed during cardiac resuscitation are related to sharp swings in positive pleural pressure, which exert a massage-like action and propel blood outwards from the heart into the systemic circulation.

It is to be however noted that the reduction in afterload effect produced by a positive intrapleural pressure during the inspiratory phase of positive pressure ventilation is negated by the obstruction to venous return caused by the inspiratory rise in intrapleural pressure. In fact the sum effect is a decrease inspiratory cardiac output because of decreased venous return (see Chapter Mechanical Ventilation in the Critically Ill Patients).

Cardiac Rate and Rhythm

The rate is also important in determining cardiac output. A rate greater than 100/minute adversely affects cardiac output, and a marked bradyrhythm acts likewise. Loss of atrial kick may sharply reduce cardiac output in patients with a poor cardiac reserve. Rhythm disturbances even in a normal heart can reduce output; they can be catastrophic in diseased hearts.

HEART FAILURE

This has been dealt with at length in subsequent chapters of the book. A few basic concepts need to be stressed at this juncture.

Cardiac failure, in brief, is a failure of the pumping action of the heart. Left ventricular failure leads to two recognizable features—

1. Pulmonary edema, with or without systemic venous congestion. Pulmonary edema is associated with an increase in end-diastolic left ventricular pressure to greater than 15 mm Hg, and often as high as 30 mm Hg.
2. Poor forward flow resulting in poor tissue perfusion. Cardiac failure may produce pulmonary edema, or poor forward flow, or both. It is important to consider these two aspects of cardiac failure as separate facets, even when both are present at the same time. Death from acute cardiac failure can be due to a severe fall in cardiac output,

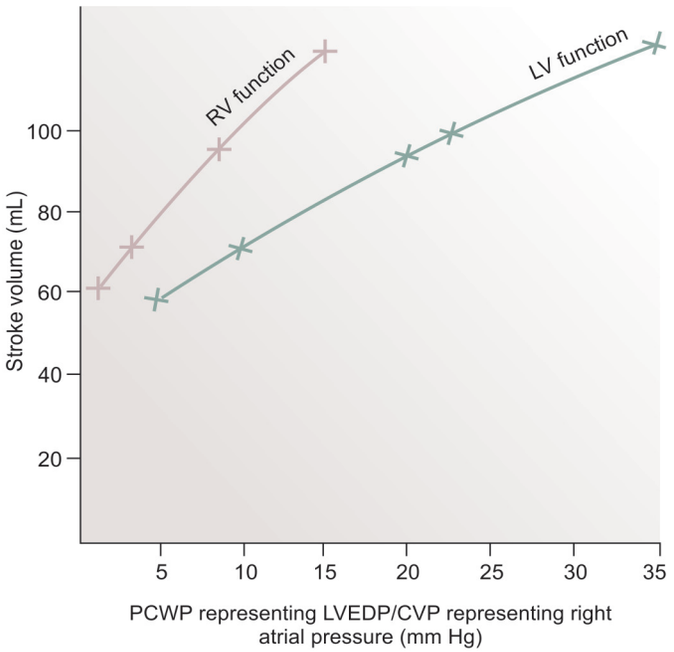


Fig. 4: Left and right ventricular function curves in an overinfused hypervolemic patient. Note that very high left and right ventricular filling pressures that cause pulmonary edema and systemic venous congestion can occur in the presence of good pump function with high stroke volumes and cardiac output

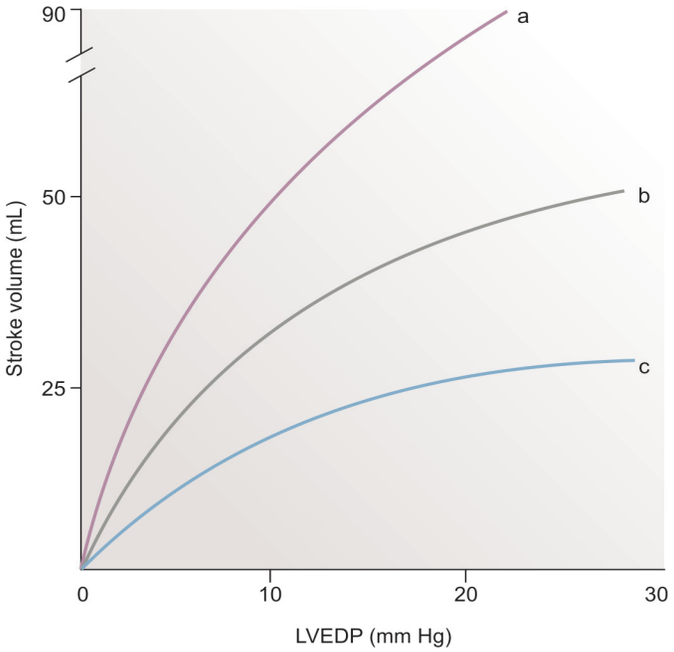


Fig. 5: Relationship of stroke volume to left ventricular end-diastolic pressure (LVEDP) in subjects with normal myocardial function (a), and in patients with moderate (b) and severe (c) left ventricular dysfunction. Note that in patients with myocardial dysfunction, a rising LVEDP produces a smaller degree of rise in the stroke volume, as compared to normal subjects

forward flow and tissue perfusion, without pulmonary edema. This can only be appreciated if the interrelation between left and right ventricular function curves is clearly understood,[10] and if both ventricles are considered as an interlocked single functioning unit.

An explanation of the two above-stated facets of acute cardiac failure has been given in the Chapter Cardiogenic Shock.

A final thought provoking statement that needs to be made, is that the presence of increased filling pressures with pulmonary edema and systemic venous congestion, does not necessarily mean failure of the heart as a pump. This situation (increased filling pressures with pulmonary edema and systemic venous congestion), can also arise in an over-transfused or over-infused hypervolemic patient. Measurements of cardiac output in such a patient shows high stroke volume and cardiac output readings (in accordance with Frank-Starling's principle), pointing to good pump function. This is illustrated in Figure 4.

Left ventricular function curves in moderate and severe left ventricular failure are illustrated below by plotting stroke volume against LVEDP, and stroke volume against increasing afterload (Figs 5 and 6).

The description of the applied physiology of the circulatory system given above has been chiefly related to the heart and its function. There are other components to the circulatory system that need to be considered.[11] These components include the following—

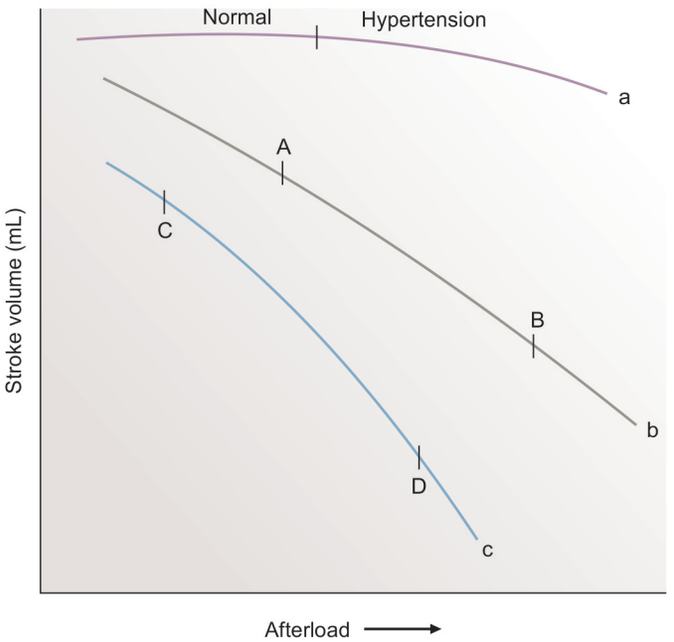


Fig. 6: Relationship of stroke volume to afterload in subjects with normal myocardial function (a), and in patients with moderate (b) and severe (C) myocardial dysfunction. In subjects with normal myocardial function, increase in afterload results in hypertension without much change in the stroke volume (SV) or cardiac output (CO). In contrast, in patients with moderate or severe myocardial dysfunction, an increase in afterload produces a sharp fall in the SV and CO, the SV being inversely proportional to the afterload or outflow resistance. It is important to note that the blood pressure may remain constant at points A and B on curve b, and points C and D on curve c, even though the SV is sharply reduced

- Intravascular volume which regulates mean circulatory pressure and venous return.
- The arteriolar bed, the tone of which chiefly determines afterload, arterial blood pressure and distribution of systemic blood flow. A marked fall in arteriolar tone causes severe hypotension. A marked rise impedes left ventricular ejection and tissue perfusion.
- The capillary network where fluid and nutrient exchange between the intravascular and extravascular compartment occurs. Damage to capillary endothelium results in increased capillary permeability with loss of intravascular volume and tissue edema.
- The venules which are responsible for 10–15% of the vascular resistance.
- Arteriovenous connections. Opening of these connections allows blood to bypass the capillaries and produces tissue hypoxia.
- Venous capacitance which contains 80% of the intravascular volume. Decrease in venous tone or increase in venous capacitance reduces mean circulating pressures, filling pressures within the heart, and effective circulating volume. Increase in venous tone or decrease in venous capacitance has exactly the contrary effects—an increase in the venous pressure and an increase in the filling pressures of the heart.
- *Viscosity of blood* Blood viscosity is chiefly due to circulating erythrocytes (hematocrit). Increase in the hematocrit means increased viscosity, entailing greater work for the heart to move blood through the circulatory system. This increase in work load may have significant clinical implications in patients with ischemic heart disease or in patients with poor myocardial reserve.

Viscosity of blood increases following a loss of plasma or fluid from the vascular system. Blood viscosity also increases following repeated packed cell transfusions, a fall in body temperature, and a decrease in the flow rate of blood. This rise in viscosity can further reduce flow through the circulation and thereby promote ischemic injury. Prevention of an undue rise in viscosity is therefore of particular importance in critically ill patients. The degree of viscosity is best gauged by monitoring hematocrit values which should not exceed 40–45% as the upper limit.

Finally, the right heart, which pumps into the low resistance, low pressure pulmonary circuit, is intrinsically and inevitably locked to the left heart which pumps into the high resistance, high pressure systemic circuit. It is a closed system, and by sheer necessity the stroke volume pumped by the two sides of the heart must be equal.

BASIC CONCEPTS OF GAS EXCHANGE

Efficient gas exchange in the lungs requires—

- An adequate alveolar ventilation evenly distributed to both lungs.
- Even ventilation-perfusion ratios of 0.8 to 1. Uneven ventilation-perfusion ratios or ventilation-perfusion mismatch is an important cause of hypoxia or poor arterial oxygenation. A ventilation-perfusion mismatch is characterized clinically and physiologically by two features: (1) An increase in dead space—ventilation of unperfused or poorly perfused alveoli which are hyperventilated in relation to the blood perfusing them; (2) an increase in venous admixture, i.e. perfusion of atelectatic alveoli causing a true right to left shunt. Alveoli which are hypoventilated in relation to blood perfusing them, also contribute to a shunt effect.
- Diffusion of oxygen across the alveolar wall into the capillaries perfusing the alveoli, and of carbon dioxide from the capillaries out into the alveolar space. A severe diffusion defect may contribute to a low PaO_2 but is hardly ever its sole cause. Most pathologies producing a diffusion defect also lead to an uneven compliance within the lungs and thereby to a ventilation-perfusion mismatch.

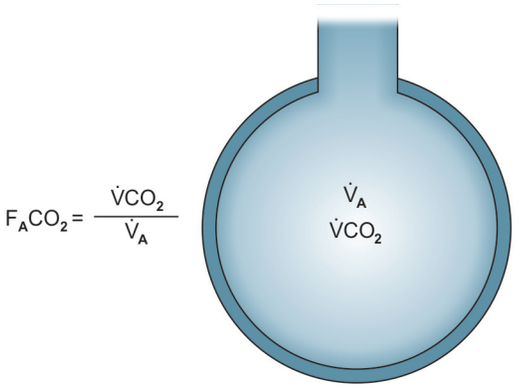


Fig. 7: Concept of alveolar ventilation

Alveolar Ventilation

The pressure of CO_2 in arterial blood ($PaCO_2$) is the best indicator of alveolar ventilation. This basic fact in respiratory physiology is explained below. Consider for purposes of illustration an alveolus of volume $\dot{V}_A$ (Fig. 7). It contains a volume of CO_2 ($\dot{V}CO_2$). The fractional concentration of CO_2 (F_ACO_2) in this alveolus is given by the volume of CO_2 divided by the volume of the alveolus.

$$F_ACO_2 = \frac{\dot{V}CO_2}{\dot{V}_A}$$

The CO_2 released into the alveolus from the blood perfusing it, will be cleared from the alveolus by ventilation; the greater the ventilation the lower the concentration of CO_2 in the alveolus. The alveolar concentration will be a balance between the alveolar ventilation and the rate at which the CO_2 is evolved ($\dot{V}CO_2$).

$$F_ACO_2 = \frac{\dot{V}CO_2}{\dot{V}_A}$$

The fractional concentration of CO_2, F_ACO_2 (0.05–0.06), exerts a pressure equal to the same fraction of the barometric pressure (PB).

$$\frac{P_ACO_2}{PB} = \frac{\dot{V}CO_2}{\dot{V}_A}$$

$$P_ACO_2 = \frac{\dot{V}CO_2}{\dot{V}_A} \times 0.863$$

0.863 is the correction factor that takes into account the barometric pressure and the different units in which $\dot{V}CO_2$ and $\dot{V}_A$ are expressed. This is the alveolar ventilation equation. It shows that the P_ACO_2 is directly proportional to the CO_2 produced, and inversely proportional to alveolar ventilation ($\dot{V}_A$). If $\dot{V}CO_2$ is constant, then P_ACO_2 is inversely proportional to $\dot{V}_A$.

$$P_ACO_2 \propto \frac{1}{\dot{V}_A}$$

There is good evidence to show that $PaCO_2$ (pressure of CO_2 in arterial blood) is very close to the average alveolar PCO_2 i.e. P_ACO_2. Thus

$$P_ACO_2 = PaCO_2 = \frac{\dot{V}CO_2}{\dot{V}_A} \times 0.863$$

The $PaCO_2$ is thus inversely related to $\dot{V}_A$. A high $PaCO_2$ (>48 mm Hg) denotes hypoventilation; a low $PaCO_2$ (<35 mm Hg) denotes hyperventilation; a normal $PaCO_2$ (35–45 mm Hg) denotes normal alveolar ventilation. It should be evident from the above equation that if the normal $PaCO_2$ of 40 mm Hg is doubled to 80 mm Hg, it means that the alveolar ventilation is just half of what is normally necessary to deal with the CO_2 produced by the body. It is to be also noted that the $PaCO_2$ may rise if the $\dot{V}CO_2$ rises and if the patient for some reason cannot increase his alveolar ventilation to get rid of the extra CO_2.

Concept of Dead Space

The anatomical dead space is that constituted by the trachea and the bronchi right up to, but not including, the gas exchange unit of the lung. It is the volume of inspired air which fills the airways and is breathed out unchanged. Air entering alveoli which have no blood perfusing them, also does not take part in gas exchange and is breathed out unchanged. This is wasted ventilation and constitutes alveolar dead space. The sum of the anatomical dead space and the alveolar dead space is termed the physiological dead space, though admittedly there is nothing physiological about this dead space. Figure 8 illustrates the concept of anatomical and alveolar dead space.

Effective alveolar ventilation is only that ventilation entering perfused alveoli. Hyperventilated alveoli will contribute to the overall concept of alveolar dead space.

Ordinarily as much as 30% of tidal volume is dead space ventilation. This may increase considerably in patients with diseased lungs. The quantum of dead space can be calculated by the following equation:

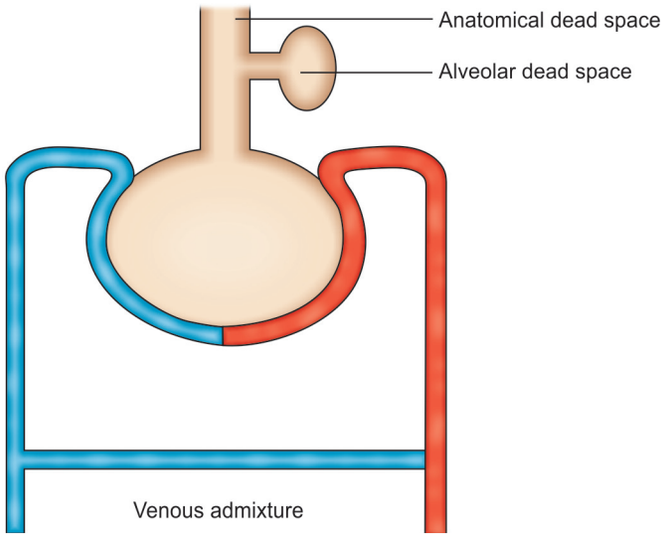


Fig. 8: Concept of anatomical and alveolar dead space and venous admixture (right to left shunt within the lungs)
Source: From Udwadia FE. Diagnosis and Management of Acute Respiratory Failure. Mumbai: OUP; 1979.

$$\frac{V_D}{V_T} = \frac{PaCO_2 - P_ECO_2}{PaCO_2}$$

where P_ECO_2 is the pressure of CO_2 in expired gas.

Alveolar Oxygen

Fresh oxygen from inspired gas enters alveoli during ventilation; the oxygen diffuses through the alveolar wall into the blood perfusing the alveoli. For any given concentration of oxygen in inspired gas (FiO_2), the alveolar concentration of oxygen (F_AO_2) will be a balance between alveolar ventilation ($\dot{V}_A$) and the oxygen taken up ($\dot{V}O_2$) by the blood perfusing ventilated alveoli.

$$FiO_2 - FAO_2 = \frac{\dot{V}O_2}{\dot{V}_A}$$

In terms of partial pressure,

$$PiO_2 - P_AO_2 = \frac{\dot{V}O_2}{\dot{V}_A} \times 0.863$$

We have already defined $\dot{V}_A$ (under Alveolar Ventilation) in terms of $PaCO_2$.

$$P_AO_2 = PiO_2 - PaCO_2 \times \frac{\dot{V}O_2}{\dot{V}CO_2} \times 0.863$$

The ratio $\dot{V}O_2/\dot{V}CO_2$ is in fact the respiratory exchange ratio R, and R in a steady state equals the metabolic respiratory quotient (RQ). Thus

$$P_AO_2 = PiO_2 - PaCO_2 \times 1/R$$

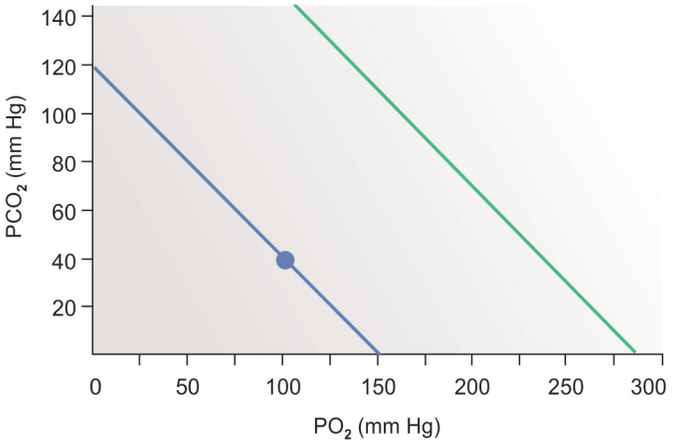


Fig. 9: O_2-CO_2 diagram. The slope of the line depends on the Respiratory Quotient (RQ, normally 0.8). For any given $PaCO_2$, the alveolar PO_2 can be read, and for any given P_AO_2, $PaCO_2$ can be read. The line to the left illustrates the P_AO_2-$PaCO_2$ relationship in the alveoli when breathing air (PiO_2 = 149 mm Hg). The circle marked on this line shows the normal alveolar PO_2 when breathing air (RQ = 0.8). The line to the right illustrates the P_AO_2-$PaCO_2$ relationship with an RQ of 0.8 when breathing 40% oxygen (PiO_2 = 285 mm Hg)

Source: From Udwadia FE. Diagnosis and Management of Acute Respiratory Failure. Mumbai: OUP; 1979.

If carbohydrates are preponderantly burnt as fuel, R = 1; if fats are burnt as fuel R = 0.7; if carbohydrates and fats are both burnt as fuel, as is usually the case, R = 0.8.

The above equation is a simplified form of the alveolar air equation. It is of great use because—

- It allows a quick determination of alveolar oxygen pressure (P_AO_2) if the PiO_2 and the $PaCO_2$ are known.
- If the P_AO_2 is known and the PaO_2 is available through an arterial blood gas measurement, the alveolar-arterial oxygen gradient can be calculated as the difference between P_AO_2 and PaO_2. The upper normal of this gradient is 15 to at most 20 mm Hg. In most normal individuals it averages 10 mm Hg.
- The alveolar equation points to a linear relationship between P_AO_2 and $PaCO_2$. The O_2-CO_2 diagram or line is further elaborated upon in the Chapter Acute Respiratory Failure in Adults (Fig. 9). From this diagram one can quickly plot the expected P_AO_2 if the $PaCO_2$ is known for any given inspired oxygen concentration. If the alveolar-arterial oxygen gradient is taken as 10–15 mm Hg, then for any given $PaCO_2$ one can read off the PaO_2. This is true provided the alveolar-arterial oxygen gradient is not abnormally increased.
- A consideration of the alveolar air equation shows that at a given inspired oxygen concentration and a given RQ, the alveolar PO_2 is dependent on alveolar ventilation. A lower alveolar ventilation would thus lead to a lowered alveolar PO_2, and hence a lowered arterial PO_2.

The alveolar air equation helps the physician to check on blood gas measurements. If the value of the measured $PaCO_2$ is taken as correct, the alveolar equation allows one to compute the P_AO_2. If the PaO_2 reported by the laboratory is higher than the P_AO_2, it is obviously incorrect.

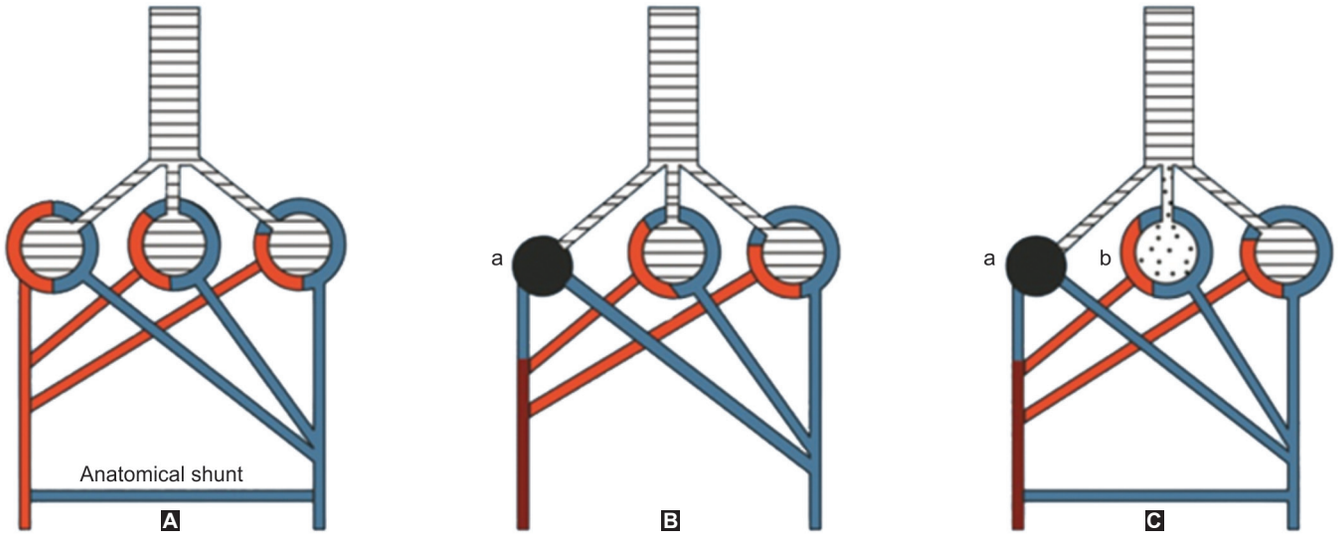
The Alveolar-Arterial Oxygen Gradient

The normal range of the alveolar-arterial oxygen gradient has already been mentioned. An increased alveolar-arterial oxygen gradient denotes an impairment of gas exchange across the alveolar capillary membrane. When however a low PaO_2 is due to hypoventilation, or is related to breathing at high altitudes, then there is no increase in the alveolar-arterial oxygen gradient since the P_AO_2 is also proportionately low. A lowered PaO_2 from any other cause (V/Q mismatch, increased shunt, impaired diffusion), is always associated with an increased alveolar-arterial oxygen gradient. Also the greater the alveolar-arterial oxygen gradient, the greater the disturbance in gas exchange within the lungs. This observation should however be viewed in its proper perspective. Thus an alveolar-arterial gradient of 20 mm Hg (upper limit of normal), when it occurs on the steep part of the oxygen dissociation curve will denote a gross disturbance in pulmonary gas exchange.

Let us consider a patient with chronic bronchitis in severe hypercapnic respiratory failure. If the P_AO_2 of this patient is 50 mm Hg and the PaO_2 is 30 mm Hg, the gradient of just 20 mm Hg (upper limit of normal) would suggest that the hypoxia is chiefly due to alveolar hypoventilation. However, at a PO_2 of 50 mm Hg the oxygen saturation is 85%; at a PO_2 of 30 mm Hg the oxygen saturation is about 55%. Thus the oxygen saturation has fallen 30% between the alveoli and the arterial blood. Normally the fall in oxygen saturation does not exceed 2%. It is evident that there is a serious disturbance in gas exchange in this patient, even though the alveolar-arterial oxygen gradient is not unduly increased.

Venous Admixture

If deoxygenated blood perfuses atelectatic alveoli and bypasses ventilated alveoli, the oxygen content of the blood leaving the lungs will be less than that leaving ventilated alveoli. This constitutes the concept of venous admixture (Figs 10A to C). Venous admixture at the bedside has two components—a true right to left shunt due to perfusion of totally atelectatic alveoli, and a shunt effect observed in alveoli which are hypoventilated in relation to blood perfusing them i.e. alveoli with low ventilation-perfusion ratios. A true right to left shunt (also called a true venous admixture) is unchanged by increasing inspired concentration of oxygen. The shunt effect produced by alveoli with lowered ventilation-perfusion ratios will however be abolished by suitably increasing the inspired oxygen concentration. The simple bedside test of noting the degree of rise in PaO_2 with 100% inspired oxygen, thus distinguishes between a true right to left shunt within the lungs, and a shunt effect produced by ventilation-perfusion inequalities. More often than not, a right to left shunt as



Figs 10A to C: (A) Anatomical shunt (portion of cardiac output bypassing pulmonary capillaries). (B) True right to left shunt in the lungs caused by perfusion of atelectatic alveoli (Alveolus a). (C) An overall shunt due to perfusion of atelectatic alveoli (Alveolus a) to a lowered ventilation/perfusion ratio causing a shunt effect (Alveolus b) and the anatomical shunt

Source: From Udwadia FE. Diagnosis and Mangement of Acute Respiratory Failure. Mumbai: OUP; 1979.

also ventilation-perfusion inequalities are present in the same patient. This is further elaborated upon in the Chapter Acute Respiratory Failure. The mathematical calculation of the venous admixture or shunt is given by the following equation:

$$\frac{\dot{Q}_s}{\dot{Q}_T} = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}$$

where $\dot{Q}_s$ is the shunt fraction, $\dot{Q}_T$ the cardiac output, CcO_2 the capillary oxygen content, CaO_2 the arterial oxygen content and CvO_2 the mixed venous oxygen content.

In practice, end-capillary oxygen content is calculated from the alveolar PO_2 by assuming that P_AO_2 is equal to end-capillary PO_2. Arterial oxygen content is either derived from the PaO_2, or estimated by an oximeter. Mixed venous oxygen content is obtained by sampling blood from the pulmonary artery through a Swan-Ganz catheter.

The normal $\dot{Q}_S/\dot{Q}_T$ is generally not more than 5%. A shunt fraction exceeding 30% is serious, and a shunt fraction approaching 50% indicates a gross degree of venous admixture, and carries a grim prognosis.

Concept of Oxygen Content and Oxygen Transport

The heart lung combine working in unison ensures oxygenation of arterial blood. But this is not enough. Blood should have an adequate oxygen content, and what is more the oxygen within the blood should be efficiently delivered or transported to tissue cells all over the body. This principle should never be lost sight of in the management of critically ill patients in the ICU.

Oxygen Content

One gram of hemoglobin (Hb) combines with 1.39 mL of oxygen at full saturation—

$$O_2 \text{ content} = 1.39 \times Hb \times \frac{\% \text{ saturation}}{100} + 0.003 \times PO_2$$

where the solubility coefficient of oxygen at 37°C is 0.003 mL/100 mL blood/mm Hg.

The percent saturation of Hb in arterial blood is related to the PaO_2. Oxygen content thus depends on Hb concentration and the PaO_2. The amount of oxygen in solution in plasma is very low (0.3 mL) due to its relative insolubility. Anemia will decrease O_2 content in a linear fashion so that a reduction in Hb from 15 g to 7.5 g/100 mL will reduce arterial oxygen content by one half, i.e. from 21 mL to 10.5 mL. However, a fall in PaO_2 from 90 mm Hg to 45 mm Hg, i.e. by 50% results in just a 20% reduction in the arterial oxygen content. It is evident that significant changes in hemoglobin concentration have a greater influence on CaO_2 than changes in PaO_2.

It is mentioned above that the PaO_2 has an important influence on arterial Hb saturation. There are two other situations (rare though they be) that can also influence Hb saturation. In methemoglobinemia, the iron in the Hb molecule is oxidized to its ferric state; reversible oxygen binding is not possible and Hb is unavailable for oxygen transport. Again in carbon monoxide poisoning, the Hb molecule avidly binds to carbon monoxide, and cannot bind to oxygen, nor offer effective transport. Both these situations are characterized by a normal Hb, a normal PaO_2, but a lowered percent Hb saturation with oxygen, a poor oxygen content and transport.

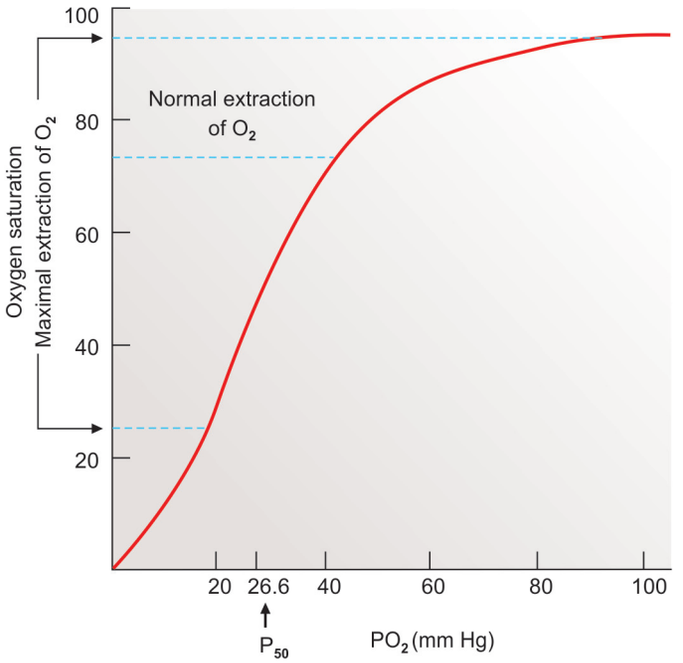


Fig. 11: The normal oxyhemoglobin dissociation curve (P_{50} = 26.6 mm Hg). At a normal PaO_2, O_2, saturation is close to 100%. At a PaO_2 of 40 mm Hg (venous blood), O_2 saturation is about 75%. Maximum O_2 extraction allows a reserve down to about 25%, corresponding to a PaO_2 of 15–20 mm Hg

Oxygen Transport

Transport of oxygen to tissues is a vital function of the cardiorespiratory system. A normal arterial oxygenation or oxygen content does not ensure adequate oxygen transport. The latter is crucially dependent on cardiac output.

$$\text{Oxygen Transport} = \text{Cardiac Output} \times \text{Arterial Oxygen Content}$$

$$DO_2 = \dot{Q}_T \times CaO_2 = \dot{Q}_T \times (1.39 \times Hb \times SaO_2) \times 10$$

It is to be noted that the dissolved oxygen component is removed and that the factor 10 converts the result to mL/minute. If the cardiac index (cardiac output/body surface area) is used instead of the cardiac output, the DO_2 is expressed as mL/minute/m^2. The normal range for DO_2 is 520–570 mL/minute/m^2.

Good critical care should therefore help provide both an adequate cardiac output and satisfactory CaO_2 to ensure the necessary oxygen transport for the needs of the tissues.

Fick Principle

The interrelationship between oxygen transport and oxygen utilization ($\dot{V}O_2$) was described by Fick in 1872.

$$\dot{V}O_2 = \dot{Q}_T \times C(a\text{-}\bar{v})O_2$$

i.e. oxygen consumption = cardiac output × arteriovenous oxygen content difference. The normal range for $\dot{V}O_2$ is 110–160 mL/minute/m^2.

An increase in oxygen consumption ($\dot{V}O_2$) by the tissues is brought about by an increase in the $\dot{Q}_T$, so that the arteriovenous oxygen content difference remains the same (normally about 4–5 mL). If for some reason the cardiac output does not increase appropriately, then the step-up in $\dot{V}O_2$ is met by an increase in oxygen extraction by the tissues, i.e. by an increase in the arteriovenous oxygen content difference. The equation in Fick's principle thus remains unaltered, and well balanced. A widened arteriovenous oxygen content difference (i.e. a lowered $P\bar{v}O_2$ and $S\bar{v}O_2$) occurs in the following conditions in critical care medicine—

- An inadequate cardiac output for tissue needs.
- A very low arterial oxygen content, as with severe anemia.
- When tissue demands for oxygen are so great, that the normal circulatory system cannot keep pace with excessive tissue demands. This could happen for example in patients with uncontrolled seizures in fulminant tetanus.

Table 1: $P\bar{v}O_2$ and $S\bar{v}O_2$ as indicators of cardiac output and tissue perfusion adequacy

$P\bar{v}O_2$ (mm Hg)	*$S\bar{v}O_2$ (%)*	*Clinical state*
36–42	71–79	Normal range
>45	>80	Septic shock
<30	<50	Lactic acidosis
<17	<20	Neural damage

Abbreviations: $P\bar{v}O_2$, mixed venous oxygen tension; $S\bar{v}O_2$, mixed venous oxygen saturation of hemoglobin.

As mentioned above, the increased extraction of oxygen by tissues from the blood, leads to a lowered $P\bar{v}O_2$ and $S\bar{v}O_2$. The normal $P\bar{v}O_2$ is 35–40 mm Hg, and the $S\bar{v}O_2$ is 75%. There is a reserve which allows for a fall in $P\bar{v}O_2$ to 15–20 mm Hg, and the $S\bar{v}O_2$ to 2–30%, in conditions characterized by a very low $\dot{Q}_T$, while still enabling diffusion of oxygen at a level that prevents cellular death (Fig. 11).

In critical care settings, the $P\bar{v}O_2$ and the $S\bar{v}O_2$ can thus act as indicators for adequacy or inadequacy of cardiac output and tissue perfusion (Table 1).

Underlying Fick's principle is the concept that $\dot{V}O_2$ is governed by tissue needs and not by oxygen delivery (DO_2). However, as will be illustrated later, below a critical level of oxygen delivery, $\dot{V}O_2$ does depend on oxygen supply.[12,13] It was earlier believed that in certain pathological states like sepsis, septic shock, acute respiratory distress syndrome, $\dot{V}O_2$ was dependent on DO_2 at all levels of oxygen delivery. The current though not universal consensus is that this is not really so (see Chapter Acute Lung Injury and Acute Respiratory Distress Syndrome). Nevertheless, the importance of ensuring adequate oxygen transport in the management of these critically ill patients cannot be overemphasized.

Oxygen Extraction Ratio (O_2ER)

The oxygen extraction ration is the ratio of oxygen uptake to oxygen delivery ($\dot{V}O_2/DO_2$). It signifies the fraction of oxygen taken up by the tissues; the normal O_2ER is 0–0.3, i.e. 20–30%. Oxygen extraction can vary. It increases when the increased demand for oxygen by tissue is not met by an increase in

cardiac output. In trained athletes the O_2ER may be as high as 0.8 at maximal exercise.[14] In diseased states like severe sepsis, multiple organ dysfunction, acute respiratory distress syndrome, oxygen extraction by tissue cells can be poor in spite of adequate oxygen supply. This is discussed at length in subsequent chapters on these topics.

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SECTION

4

Procedures and Monitoring in the Intensive Care Unit

- Procedures in the Intensive Care Unit
- Cardiac Monitoring in Adults
- Respiratory Monitoring in Adults

CHAPTER 6

Procedures in the Intensive Care Unit

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ENDOTRACHEAL INTUBATION

Endotracheal (ET) intubation can be performed orally or nasally through the larynx and into the trachea. The main indications of ET are—

- Relief of airway obstruction, e.g. facial burns, smoke inhalation, epiglottitis or vocal cord edema.
- Protection of airway, e.g. prevention of aspiration, incoordination of swallowing muscles, obtunded and comatose patients.
- Ventilatory support, e.g. acute respiratory failure, during general anesthesia, flail chest (also see Chapter Airway Management).

ORAL ENDOTRACHEAL INTUBATION

Intubation by mouth is preferred over nasal intubation as it allows a larger ET with less airflow resistance. However, oral intubation is less comfortable to the patient producing excessive secretions. Conscious patients find it difficult to tolerate the ET and they may constantly gag or bite on the tube.

Instrument tray for oral ET should include the following—

- Laryngoscope with both straight (Miller) and curved (MacIntosh) blades, ranging from size 0 (neonates) to 4 (adults). It is vital to check that the blades attach to the handles well and that both batteries and the bulb are in place, so that it lights sharply (brightly) on snapping open the blades of the laryngoscope.
- ET tubes, come in sizes ranging from 2 to 10. The size refers to internal diameter (ID) of the tube in millimeters and it comes in 0.5 mm increments (Table 1). Along the body of the tube, a radio-opaque line runs lengthwise for the proper verification of tube placement on X-ray. Markings in millimeters are also shown along the body for easy determination of the depth of insertion. Distal end of the tube has a cuff, which is connected to a balloon at the proximal end which is used to regulate volume of air in the cuff via a 10 mL or larger syringe.

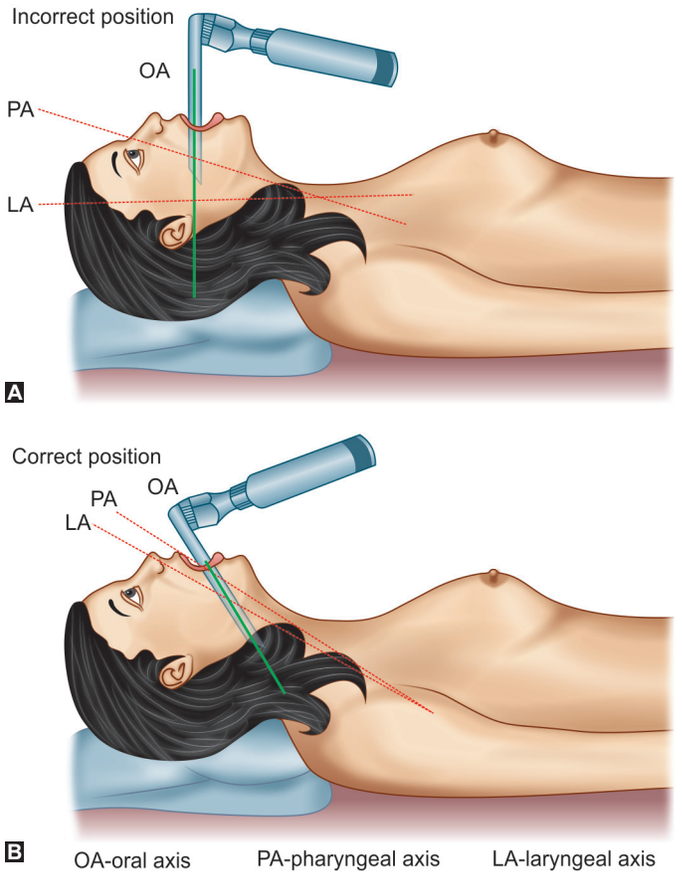
  Portex tubes are the most commonly used tubes, but stiff rubber ET tubes (Rush) should also be handy, as they may prove useful in difficult intubations.
- Syringes, lubricants, securing tape, flexible guiding stylet, topical anesthetic, Magill forceps, suction catheters and an AMBU bag with proper connections should also be provided.

Procedure for Oral Intubation

After assessing the patient, clearing the mouth of any foreign body, such as dentures and checking the ET and laryngoscope, place the patient in sniffing position by tilting the head back so that the oral, pharyngeal and laryngeal axes are aligned. This is usually achieved by raising the head by about 10 cm with pads under the occiput while shoulders remain on the table (Fig. 1). Always explain the procedure to the patient and reassure him if he is conscious. Next, lubricate the deflated

Table 1: Estimation of size of ET

Patient	*Size (mm)*
Neonates <1,000 g	2.5
Neonates 1,000–3,000 g	3–4
Child 1–2 years	4–5
Child 2–12 years	4.5 + (age/4)
Average adult female	7.5–8.5
Average adult male	8–9



Figs 1A and B: Positions for endotracheal intubation

cuff at the distal end of the ET. It is always best to ventilate and preoxygenate the patients with 100% O_2 using an AMBU bag and a face mask. If ET intubation is not successful in 30 seconds, ventilate the patient once again using 100% O_2. Now hold the laryngoscope handle with the left hand (Fig. 1) and insert the blade into the right side of the mouth; sliding the blade to the base of the tongue and simultaneously swapping the blade to the left. Maneuver the tip of the straight (Miller) blade underneath the epiglottis, or the tip of the curved McIntosh blade at the vallecula. Lift the handle and blade up anteriorly to display the tongue and attached soft tissues. Now you should be able to locate the larynx and vocal cords and under direct vision insert the ET. Check for airflow at the proximal end and auscultate for breath sounds and then inflate the cuff. It is always best to confirm proper tube placement with an X-ray chest.

NASAL INTUBATION

The initial preparations and head positioning are the same as for oral intubation. This is a blind technique, and intubation is done by inserting the ET tube (size smaller than one would use for oral intubation) through a nostril. This should be advanced slowly and when the distal end can be seen through the mouth it is laryngoscopically guided by Magill forceps into the trachea. In a fully conscious and cooperative patient, the tube may be advanced slowly during inspiratory efforts and when the distal end approaches the trachea air movement can be felt and heard through the tube. At this point, the tube is gently pushed into the trachea releasing a gush of air almost audible through the tube. Tube placement should be immediately confirmed by ensuring bilateral breath sounds and later by X-ray chest.

COMMON PROBLEMS AND ERRORS OF ET INTUBATION

The commonest error is wrong placement of the tube. The tube could be wrongly pushed so that its tip lies in a bronchus (usually the right bronchus) instead of the trachea (above the carina). If undetected and uncorrected, this could cause a disastrous collapse of the unventilated lung. The tube could also lie with its tip in the oropharynx, or pushed down into the esophagus instead of the trachea. This is immediately detected by the absence of breath sounds on manually ventilating the patient. Instead one can see the stomach getting distended. It is mandatory to always confirm correct tube placement by auscultating both lungs for good air entry and confirming the location of the tip by an X-ray of the chest. Measurement of the end-tidal CO_2 ($ETCO_2$) is also useful in confirming the placement of the ET.

The ET should be *secured* firmly to avoid displacement. Usually an adhesive tape or a commercially made harness is used but too often moisture and secretions gather between the tape and skin and loosen the tape creating a risk of self-extubation. It is hence important to check the fit frequently and to use adhesive tapes of good material.

Ischemic injury and tissue necrosis may occur if the *cuff pressure* is too high and exceeds the capillary perfusion pressure in the trachea. The ET pressure should be less than 25 cm H_2O to allow adequate capillary pressure and for patients with hypotension, it should be kept even lower. To ensure and monitor proper cuff pressure, a Posey cufflator with an inbuilt manometer is available.

To avoid suction-induced hypoxia, the patient is preoxygenated and the suction time kept less than 15 seconds.

Certain specific problems can be encountered when using the laryngoscope, especially in oral intubation. A common mishap is aspiration of dentures if one has forgotten to check and remove them. Trauma to the teeth and soft tissue can also occur. This can be avoided by being more gentle and careful during the procedure. Also, with experience, one can guide and maneuver the tube over the laryngoscope's blade with greater skill, especially in difficult intubations. Complications of ET intubation have been dealt with in the Chapter Airway Management.

The general criteria for extubation are listed in Box 1. For care of ET tube and extubation see Chapter Airway Management.

Box 1: General criteria for extubation

- Rapid breathing test—
  f/V_T <100 min/L (VT is tidal volume in liters)
- ABG—
  Acceptable blood gases on FiO_2 <0.4 and spontaneous minute ventilation <10 L/min. PaO_2/FiO_2 >250 mm Hg
- Ventilatory pressure—
  Maximum inspiratory pressure > –20 cm H_2O
  VC >15 mL/kg
- Cardiopulmonary assessment—
  Stable cardiac and pulmonary status

Cricothyroidotomy[1-3]

Cricothyroidotomy is a bedside surgical procedure, which can be life-saving when performed for the correct indication.

Indications

Surgical cricothyroidotomy is indicated in all patients who require immediate intubation, which cannot be performed because of the following problems—

- Severe maxillofacial problems.
- Poor visualization of vocal cords due to local edema, blood or abnormal anatomy.
- Cervical spine lesions requiring immobilization and where the neck cannot be manipulated.

Equipment

- Kelly or Crile clamp.
- Scalpel.
- Antiseptic solution and surgical gloves.
- Tracheostomy tube (no. 6 size).

Procedure

The most important part of the procedure is the correct identification of the cricothyroid membrane. The cricoid cartilage is the first small notch on sliding the index finger upward in the midline from the sternal notch. The firm membrane between it and the thyroid cartilage (Adam's apple) is the cricothyroid membrane.

The patient should be supine with the neck in neutral position and the thumb and index finger of the non-operating hand should stabilize the trachea-laryngeal complex by firmly fixing the thyroid cartilage as shown in Figure 2. A 3–4 cm vertical or transverse incision should be made through the skin, dermis and cricothyroid membrane. This should identify the cricothyroid space, which should be dissected and opened transversely by means of a sharp knife. In spontaneously breathing patients, a successful incision of the membrane should immediately be followed by a gush of air. The index finger should be immediately inserted in the space and a clamp is next inserted to spread the membrane and enlarge the space. Now by pulling the clamp upward the trachea is elevated and a tracheostomy tube (no. 6 size) is inserted under the clamp and the clamp is removed.

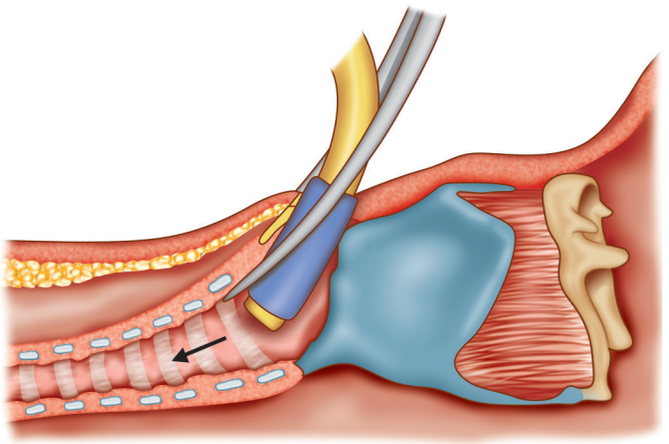


Fig. 2: Procedure for cricothyroidotomy

Complications

- Laceration of the anterior jugular veins is a potential complication because of their paramedian and superficial location which is in close proximity to the incision. With a vertical incision, the likelihood of injury to the veins is less. However, in the event that the vein is injured, the bleed can be stopped with manual pressure or may require suture ligation.
- Oropharyngeal injury is a major complication and can occur if the scalpel penetrates the posterior wall of the trachea. This is avoided by dissecting the cricothyroid membrane with a finger or a blunt clamp but never by using a sharp and penetrating instrument like a knife. Observing proper fixation of the thyrolaryngeal complex and taking an adequate incision enabling good visualization of the thyroid and cricoid cartilage is very important in avoiding this mishap.
- Bleeding from adjacent structures is probably the most common problem but can be avoided or minimized by staying in the midline during the surgery.

Percutaneous Dilatational Tracheostomy

Indications

- As an elective procedure when it is desirable to shift from ET intubation to a tracheostomy. In this situation, the ET tube is left in position and removed only at the appropriate time.
- To secure an airway in an emergency, when ET intubation fails or when ET intubation is not considered feasible for technical or anatomical reasons.

It is to be noted that though percutaneous dilatational tracheostomy (PDT) is perhaps more expedient than a formal tracheostomy in a dire emergency, it carries a greater risk of perioperative cardiopulmonary complications and death. It requires not only expertise, but also experience and should not be performed if these are not available. PDT should also be avoided in children and in obese patients.

Procedure

The two most commonly available kits for this procedure are—

1. Cook kit and
2. Portex kit.

In an elective PDT, the ET tube is left in place throughout the procedure and removed only at the appropriate time. The procedure begins with a small 2 cm vertical incision made mid-distance between the cricoid cartilage and sternal notch. After separating the pretracheal muscles, the trachea is palpated through the incision. Next a needle attached to a 10 mL syringe filled with saline is digitally guided and inserted in the midline through the second and third tracheal rings, with constant suction on the syringe while inserting. On entering the trachea bubbles of air are aspirated into the syringe and at this point it is vital to hold the needle still and disconnect the syringe (Fig. 3).

Once the needle is stabilized a guidewire is gently passed through its lumen and the needle then withdrawn. A dilator is next passed over the guidewire to dilate the existing tract. After removing the dilator a guiding catheter is passed over the guidewire and inserted into the trachea. Progressive dilatations are now done starting from 12 Fr dilator up to the largest 36 Fr and these are all done over the guidewire and the guiding catheter. Serial dilatations should be done at a correct angle and with minimal force to avoid injury to trachea or creating a false pretracheal passage. After the largest dilator is inserted and withdrawn a digit is inserted through the incision into the trachea for palpating the ET. An assistant is asked to withdraw the ET slowly and stop withdrawal when the tip of the tube is right over the palpating finger. A Shiley tracheostomy tube (no. 8) fitted snugly with a 28 Fr dilator is now introduced over the guidewire and guiding catheter complex into the trachea. Once the tracheostomy tube is in place the guidewire, the guiding catheter and the 28 Fr dilator are all withdrawn. The balloon of the tracheostomy tube is inflated and the tube placement is confirmed by auscultation and only then the ET is removed.

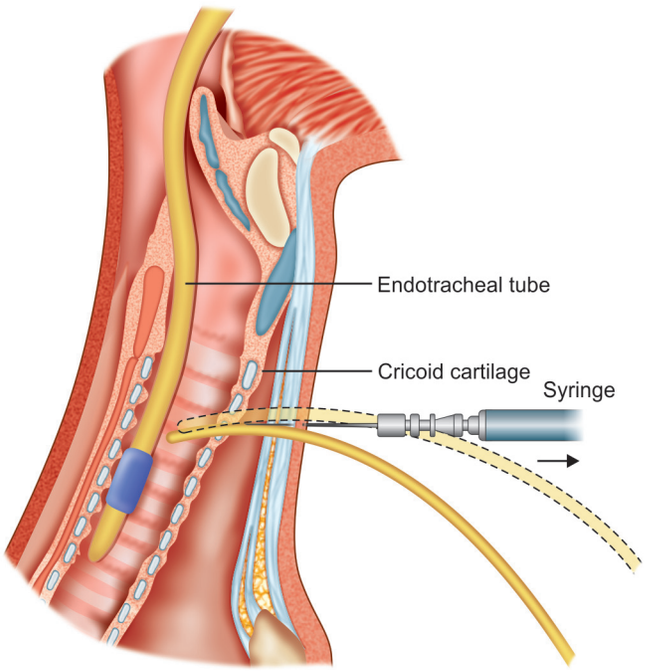


Fig. 3: Procedure for percutaneous dilatational tracheostomy (PDT)

Complications

- Incorrect placement of needle. This may be avoided by introducing the needle under digital guidance.
- Perforation of the posterior wall of the trachea by dilators. This can be avoided by not applying unnecessary force to the dilator whilst putting it into the trachea and placing the dilator at the correct angle.
- Bleeding into the trachea. This can occur with a low placement of the tube causing injury to the thoracic inlet vessels; though rare, the most lethal is an injury to the innominate artery. If such a complication should occur direct pressure should be applied until the patient is moved to the OT for surgical repair.

The sophistication, ease and safety of this technique have made it an increasingly popular procedure that can be performed by a trained intensivist at the bedside. There is however an ongoing debate whether this is truly as safe as it was predicted and whether it is cost effective. In any case, it is always an asset for an intensivist or the on-call surgeon to be familiar with the technique.

PERCUTANEOUS TECHNIQUES FOR CENTRAL VENOUS CATHETERIZATION[4]

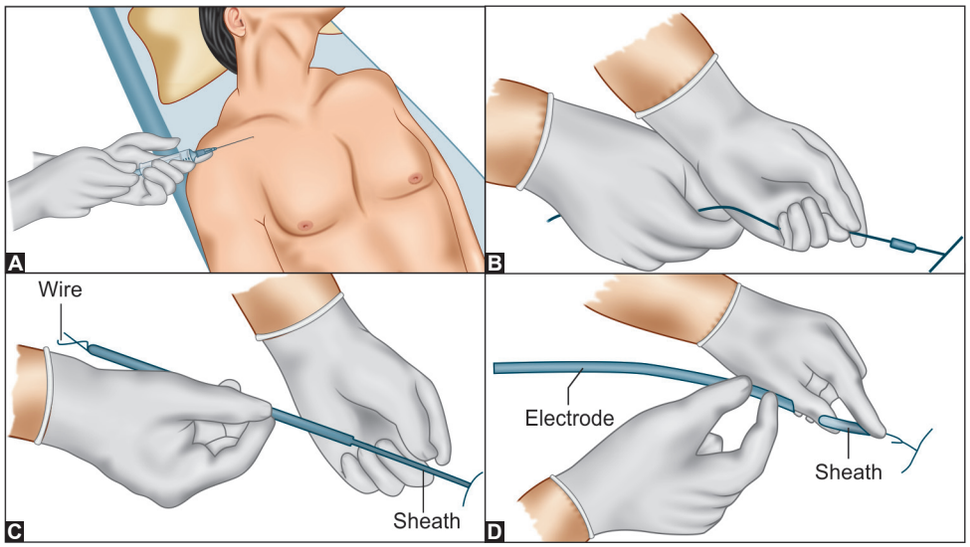
Presterilized sets of special catheters with associated devices are now available as presterilized sets for percutaneous entry into larger veins, e.g. the subclavian, internal jugular, femoral or brachial veins.

Catheter-over-needle devices are most commonly used, and are designed to eliminate the risk of the needle cutting through the catheter; the greatest danger of catheter-through-needle devices is the shearing of the catheter if it is accidentally withdrawn through the needle. These devices consist of catheters of variable length, which can be easily passed through the needle lumen, and can be advanced through the peripheral veins into the central veins.

Both these devices allow placement of a catheter in the central veins by direct puncturing of the vessel. However, if a Swan-Ganz or a pacing catheter needs to be passed through the vein, one may have to use special Introducer Sets. These are usually expensive units consisting of a needle, guidewire and a dilator over, which a polythene sheath is tightly wrapped. These sets require use of the modified Seldinger technique for introduction of the wide-bore introducer sheath in the vein, through which the catheter can then be passed.

Modified Seldinger Technique (Figs 4A to D)

The site of the puncture is infiltrated with 1% lidocaine. The vein is cannulated percutaneously with an 18-gauge thin-walled needle, following the appropriate landmarks and techniques for individual veins as described later.



Figs 4A to D: Modified Seldinger technique of inserting a guidewire and introducer set via subclavain vein puncture. (A) Direction of needle and site of puncture; (B) Insertion of guidewire; (C) The introducer sheath (with dilator) is first advanced over the guidewire. Next, with the sheath well in, the guidewire and dilator are removed; (D) An electrode or catheter is inserted through the sheath
Source: Vakil RJ, Udwadia FE. Diagnosis and Management of Medical Emergencies, 3rd edition. Bombay: OUP; 1988.

Blood is aspirated from the needle to confirm its entry into the vein, following which the soft end of a J-tip 0.035 inch guidewire is inserted through the needle, and advanced into the superior vena cava (if the subclavian or internal jugular vein is used), or the inferior vena cava (if the femoral vein is used). The guidewire should slide effortlessly through the vein, and should never be forced. After the guidewire is satisfactorily inserted (check that it is not inserted too far in as it may produce ventricular ectopics), the introducer needle is removed, and a small nick is made near the puncture to facilitate the passage of the dilator. The tapered vein dilator carrying an introducer sheath is then advanced over the guidewire with a twisting motion through the skin and subcutaneous tissue, into the vessel. Finally, the wire and dilator are removed, leaving the wide-bore introducer sheath in the vein, through which the Swan-Ganz or pacing catheter can be passed. The sheath should be secured well with sutures. Some of the introducer sheaths have a one-way valve at the proximal end to prevent backflow of blood, and a side port to allow continuous infusion of fluid to prevent clotting. Throughout this procedure, care should be taken to ensure that the proximal end of the guidewire always remains outside, and does not migrate into the vein. If for any reason, during the procedure, the guidewire needs to be removed and reinserted, the whole procedure should be repeated from the beginning; the needle should never be reintroduced over the guidewire as it can shear the wire.

Techniques for Specific Veins

Subclavian Vein Catheterization

The patient lies flat or in a slight head-low position. Correct positioning is important; both arms should be stretched straight by the sides, and the patient should be lying on a firm flat surface so that both the shoulders are in the same plane. The site of puncture is a point just below the junction of the middle and inner thirds of the clavicle.

The skin is now punctured at the selected site, with the point of the needle directed toward the suprasternal notch; the plane of the needle should be horizontal to the ground and parallel to the parietal pleura (Fig. 5). The needle is advanced with a gentle suction on the syringe until the subclavian vein is entered, often with a distinct give. It is sometimes necessary to slightly change the angle of the needle, in which case it is always essential that the needle is completely withdrawn before re-entering in a new direction. Once the needle is in the

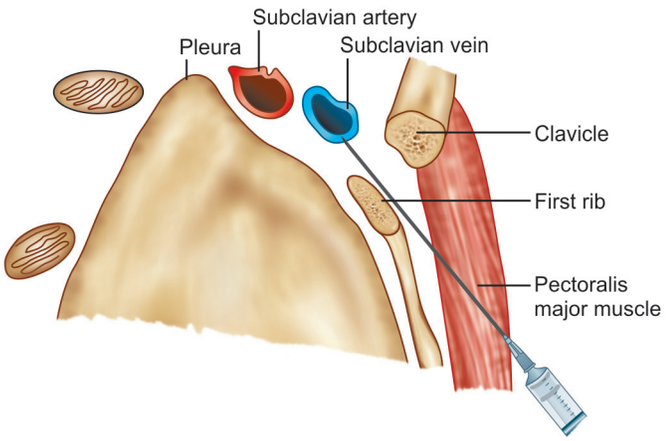


Fig. 5: Percutaneous subclavian vein puncture: anatomical relationship of the subclavian vein
Source: Vakil RJ, Udwadia FE. Diagnosis and Management of Medical Emergencies, 3rd edition. Bombay: OUP; 1988.

vein, depending on the catheter design, proceed either with the modified Seldinger technique, or directly introduce the catheter through the needle, or slide it from over the needle.

Complications Pneumothorax is the commonest major complication of this procedure. The incidence of pneumothorax can be reduced by avoiding large-bore needles, multiple punctures, and by disconnecting the ventilator at the time of venipuncture. Other serious complications include air embolism, catheter-induced infection, perforation of the superior vena cava and hemothorax (due to accidental puncture of the subclavian artery).

Internal Jugular Venipuncture[5]

The patient is placed in the Trendelenburg position, and the skin cleaned and carefully draped. The site of puncture is located two finger breadths above the clavicle at the outer border of the sternomastoid, with the patient's head rotated to the opposite side. The needle with the syringe attached is directed toward the suprasternal notch. Aspiration of blood indicates entry into the vein. Air embolism and thrombophlebitis are the main complications encountered in this procedure. Accidental puncture of the internal carotid artery can also occur. Pneumothorax is rarely observed following this procedure.

Femoral Venipuncture[6]

The femoral vein can also be entered percutaneously. The site of puncture is below the inguinal ligament, just medial to the point where the femoral artery pulse can be palpated. Wound infection is generally more common, and there is an increased risk of thrombophlebitis when the femoral vein is used.

Arterial Catheterization[7]

Except in unavoidable circumstances, it is wise to choose the radial artery for catheterization,[8] as the risk of occlusion of a proximal artery, such as the femoral or brachial, could prove disastrous. It is vital to assess the patency of the radial artery by Allen's test prior to catheterization, as it is important to be sure that a competent ulnar artery is present. This is done as follows—

- The examiner compresses both arteries, when the patient makes a tight fist to squeeze all the blood out of the hand.
- The patient then extends the fingers, and the examiner observes the blanched hand.
- Compression on the ulnar artery is released, and the examiner observes the hand filling with blood. If filling does not occur, the ulnar artery is presumed to be nonfunctional.

Technique of Radial Artery Catheterization

The wrist is hyperextended and a small area over the radial artery is cleaned and prepared with alcohol and betadine solution. A small area on both sides of the artery is anesthetized with 1% lidocaine solution. The artery is palpated with the forefinger and middle finger of one hand, and the needle (we prefer a catheter-over-needle device), is now inserted percutaneously toward the artery. As the needle touches the vessel wall the arterial pulsations are damped; the needle is now advanced further through the wall into the lumen of the artery. As soon as the blood gushes out, the catheter is advanced slowly over the needle, and the needle is then removed. The catheter hub is attached to a continuous flush system (Intraflo) via a pressure tubing. The hub of the catheter should be fixed firmly to the skin, and an antibiotic ointment dressing applied over the point of arterial puncture.

Maintaining tight compression over the puncture site, and proper attention to asepsis will go far in avoiding the two commonest complications of arterial puncture, viz. local hematoma formation and infection. Clotting of the catheter can be prevented by using a low dose continuous heparin infusion.

TEMPORARY BEDSIDE PACING[9,10]

The most commonly used external pulse generators are ventricular inhibited (demand) units; these generally permit programming of the rate between 50–150/minute, and have a sensing facility, which allows use in full demand or in the asynchronous mode. Temporary pacing leads (both unipolar and bipolar) are available in various sizes (5–7 Fr); however, pacing with a bipolar lead is more common.

In extreme emergencies, transthoracic temporary pacing can be done by introducing a wire into the myocardium through a chest wall needle.

Technique

Lead Insertion

The pacing electrode may be introduced into the vein percutaneously or by venous cut down. The commonly used veins are the basilic vein in the antecubital fossa, the subclavian, internal jugular or femoral veins. The choice of vein depends on the doctor's expertise. However, it should be noted that inserting a lead through a cut down in the antecubital fossa usually involves considerable manipulation, whereas insertion through the internal jugular, subclavian or femoral veins provides a more direct route to the atrium and requires less manipulation. A left subclavian or femoral approach is preferable, as the curvature of the lead is shaped so as to allow an easier entry into the right atrium and from there into the right ventricle.

The electrode tip is advanced to its final position at the right ventricular (RV) apex, either under fluoroscopic guidance or by intracardiac ECG monitoring. However, not many hospitals in developing countries can afford a portable image intensifier, and not all critically ill patients can be shifted to the X-ray department. Hence, one should learn to position the lead by intracardiac electrogram monitoring.

Lead Positioning (by Intracardiac Electrogram Monitoring)

After entering the vein, the proximal tip of the electrode is attached to lead V_1 of the standard ECG machine with the aid of an alligator clip cable. Lead V_1 shows a prominent P wave as the pacing electrode advances toward the heart, being inverted in the high atrium and biphasic in the midatrium. Entry of the pacing electrode into the right ventricle is facilitated by forming a loop in the right atrium, and then rotating the catheter either clockwise or anticlockwise, so that the distal end of the lead flips across the tricuspid valve. As the electrode tip crosses the tricuspid valve and enters the RV cavity, the intracardiac ECG changes markedly. An rS ventricular pattern with very deep S and deep T waves appears; this may necessitate decreasing the standardization by half. When the catheter tip abuts on the endocardial surface of the RV wall, an elevated ST segment is observed due to a current of injury. Ventricular ectopic beats are commonly observed when the catheter tip traverses the tricuspid orifice; rarely ventricular fibrillation may occur, necessitating withdrawal of the pacing catheter tip and prompt defibrillation if necessary (Fig. 6).

Once the electrode is correctly positioned at the apex of the right ventricle, the lead is connected to the battery-operated pacemaker box. It is now necessary to test the electrical threshold of stimulation, and if the pacemaker is set for demand mode, the ability of the electrode tip to sense the R waves.

The electrical threshold is tested by slowly reducing the amperage of the pacemaker till the paced QRS complexes disappear, and only the pacemaker spikes and the patient's own spontaneous beats are present. The amperage is now slowly increased till pacing is re-established, this being the electrical threshold. If pacing does not occur at an electrical threshold of less than 2 mA, it may be best to reposition the electrode. The pacemaker rate depends on the clinical needs of the patient, and is generally kept between 70–80 beats/minute.

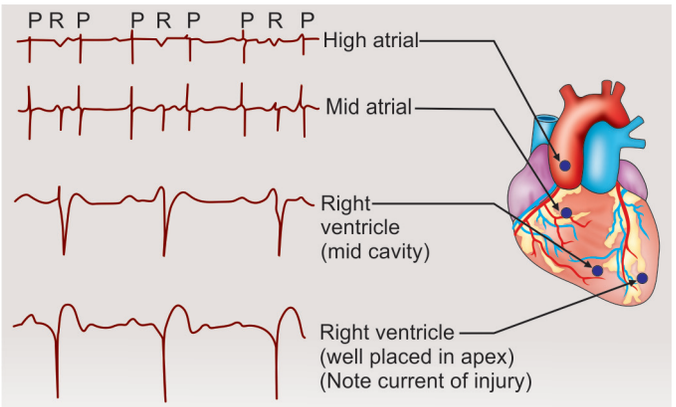

P R P P R P P R P
High atrial
Mid atrial
Right ventricle (mid cavity)
Right ventricle (well placed in apex) (Note current of injury)

Fig. 6: Bedside intracardial pacing characteristics of intracardiac electrocardiograms

Source: Vakil RJ, Udwadia FE. Diagnosis and Management of Medical Emergencies, 3rd edition. Bombay: OUP; 1988.

To test the sensing function in the demand mode, the sensing dial is turned clockwise (in most pulse generators) to full demand mode, and then gradually turned toward the asynchronous mode till sensing is just lost. In this way we can measure the R wave amplitude to ensure adequate sensing of cardiac activity. Unfortunately, most temporary pulse generators do not write the exact values over the dial, but the full demand mode would usually indicate 1 mV, and the opposite asynchronous mode about 20 MV. Ideally an R wave less than 6 mV should be sensed. If this does not occur, indicating that the sensing threshold for the R wave exceeds 6 mV, the lead should be repositioned.

Indications for Temporary Pacing

Temporary pacing with an external pulse generator remains an important therapeutic option, and an experienced physician can readily initiate temporary pacing in emergency situations. The two main indications for this procedure are as follows—

Therapeutic

These can be broadly classified into three major groups—

1. In patients with life-threatening bradyarrhythmias (e.g. severe sick sinus syndrome, second degree, third degree, or high degree AV blocks, slow junctional or idioventricular rhythms), where it is mandatory to maintain an adequate cardiac rate.
2. In patients with symptomatic bradycardias or symptomatic conduction defects. These patients commonly present with recurrent Stokes-Adams attacks, syncope or near syncope, which may be due to second or third degree AV blocks or sinus dysfunction.
3. In selected cases with intractable tachyarrhythmias, where overdrive temporary pacing is used to terminate or prevent the tachycardia. However, this is only a temporary measure and helps to buy time till the tachycardia can be controlled by medical therapy.

Prophylactic

Temporary pacing may help in preventing the occurrence of sudden death in the following subsets of patients with acute myocardial infarction—

1. In patients with inferior myocardial infarction associated with Wenkebach's phenomenon or a second degree heart block, where the possibility of a complete heart block is anticipated.
2. In patients with extensive anterior wall infarction with recently acquired bifascicular blocks (especially those with right bundle branch block associated with a block in the left posterior inferior division, or in patients with a new bundle branch block associated with transient complete heart block).
3. Patients with underlying conduction defects, such as chronic heart blocks, bifascicular blocks or brady-arrhythmias, who are otherwise asymptomatic, may require temporary pacing at the time of major surgery.

Complications of Pacing

Infection at the local site, phlebitis and thrombosis of peripheral veins are the commonest complications. Systemic infection, lead perforation through the ventricular wall, diaphragmatic pacing and pacemaker-induced arrhythmias are other major complications that need to be promptly recognized and treated.

Pacing Failure

Malfunction of a temporary pacemaker may result in complete or intermittent failure to capture. Here the ECG will show regular pacing spikes without pacemaker captures; the commonest cause of this is a displaced lead, which will require repositioning. A total lack of output on the other hand, manifests on the ECG as absence of both spikes and pacing captures, and is generally caused by either a loose connection, lead fracture, battery failure or a fault in the pacemaker itself.

Sudden cessation of pacing in a patient with marked bradyarrhythmia or absent intrinsic rhythm due to any of the above-mentioned causes can result in cardiac arrest. In such an eventuality, the first priority should be the re-establishment of cardiac rate and rhythm. All ICU personnel should be familiar with the following emergency protocol in case of sudden pacemaker failure—

i. Check if patient is asymptomatic.
ii. Check whether all generator connections are tightly fitted.
iii. Increase pulse generator output to highest setting.
iv. Replace pulse generator battery.
v. Turn patient on left side.
vi. If cardiac arrest occurs, continue cardiopulmonary resuscitation till such time as the fault is corrected, or the lead is repositioned.

Other less common causes of pacemaker failure are failure to sense, and RV perforation. Failure to sense occurs if the pacemaker continues to function at a fixed rate, even though it is set on demand mode. The commonest cause of sensing failure is a slight displacement (may be only a few millimeters) of the electrode tip; it is mandatory that the lead be repositioned immediately to avoid a potential though rare danger of ventricular tachycardia or fibrillation. Perforation of the RV by the electrode tip leads to a total loss of pacing, or frequent failure to capture and to sense, and is seen on the ECG as a marked change (>90 degrees) in the electrical axis of the pacemaker spike, or in the QRS axis of the paced ECG. Stimulation of the phrenic nerve may occur, producing contractions of the diaphragm or of the intercostal or abdominal muscles. A pericardial friction rub is heard at times; hemopericardium with cardiac tamponade is a rare complication.

CHEST TUBE DRAINAGE[11]

Intercostal tubes are used to aspirate air or fluid from the intrapleural space. At times, as in a tension pneumothorax, intercostal drainage needs to be performed as an emergency procedure. This is basically a bedside procedure which can be performed easily and safely in the ICU, and all senior resident doctors looking after ICU patients should familiarize themselves with the techniques of chest tube insertion.

Emergency Procedure

A tension pneumothorax can cause a very rapid hemodynamic deterioration, leading to cardiopulmonary collapse and death, if not relieved immediately. Inserting a chest tube may be time-consuming, and a needle should be immediately inserted to relieve the pressure. A 16 gauge angiocath (catheter-over-needle device) is inserted in the second intercostal space, anteriorly in the midclavicular line. Once the pleural space is penetrated, the air under tension is immediately released and the pneumothorax is decompressed. At this point the needle is removed, leaving the catheter in the pleural space. The catheter hub is connected to a long tubing, the other end of which is placed underwater so that the air can bubble out in a more controlled manner. This is however a temporary procedure, and preparation for an immediate chest tube placement must be made for more efficient decompression of the pnemothorax.

Drainage System

A conventional 2 or 3 bottle system is commonly used for evacuation of intrapleural air and fluid as shown in Figure 7. Each bottle is placed in a series. The first is the trap bottle which collects the fluid from the pleural space and at the same time allows air to pass through to the next bottle, i.e. the water seal bottle. This second bottle acts as a one-way valve, allowing air to escape from the pleural space, but preventing atmospheric air from entering the pleural space when negative pleural pressure is created during inspiration. The inlet tube in the second bottle is placed underwater, thereby creating a back pressure on the pleural space, which is equal to the submerged depth of the inlet tube. This back pressure, called the water seal pressure, is usually 1–2 cm of H_2O, and should ideally suffice to reinflate the lung. Further negative pressure, if required, can be provided by applying a central suction. However, for reasons of safety, a third bottle called the suction control bottle, is added in the series. This bottle has an underwater tube, which is open to the atmosphere, as shown in Figure 7. The depth of this tube column determines the safety, by setting a limit on the negative pressure that is imposed on the pleural space. For example, if this column is 15 cm under water, any negative pressure greater than –15 cm H_2O from a central suction, will result in a constant bubbling of air into the third bottle, and prevent the subatmospheric pressure from exceeding –15 cm H_2O.

Procedure for Chest Tube Insertion

A chest tube tray containing sterile drapes, local anesthetic, medium and large Kelly clamps and other material, such as sutures, antiseptic solution and dressing materials, should be

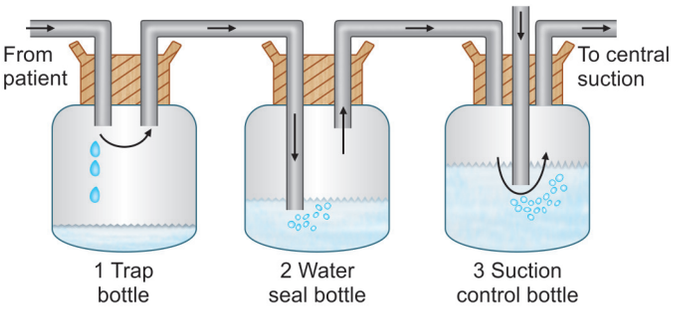


Fig. 7: Three-bottle pleural drainage system (see text for discussion) (→ = flow of air)

kept ready. Chest tubes of various sizes are available from 12 Fr to 42 Fr. Larger sized tubes are used for traumatic hemothorax or hemopneumothorax, whereas smaller tubes ranging 12–22 Fr may be used for spontaneous pneumothorax. The tube itself is made of a transparent material, with multiple side holes over the distal third of its length; there is also a radio-opaque strip at the distal end of the tube to mark its placement in the pleural space. These tubes are available in a trocar for tunneling through the intercostal space. In case these special tubes are not available, a simple Malecot's catheter may be used.

The patient should lie flat with the involved side elevated by a pillow, and arms flexed over the head. After infiltrating the skin with lidocaine (1% or 2% solution), a skin incision is made at the appropriate site of tube insertion, which is usually in the fifth or sixth intercostal space in the anterior axillary line. Some operators prefer the second intercostal space in the midclavicular line, but the penetration of muscles and breast tissue is more difficult at this site. After incising the skin at the appropriate puncture site, the muscles and tissues are penetrated by either a blunt dissection using clamps and index finger to enter the pleural space or the tube is directly inserted with the help of a trocar. Rotating movements are used whilst advancing the tube with the trocar.

Once the pleural space is entered, the tube is advanced upward in the direction of the apex for treatment of a pneumothorax, and toward a post-basal position for drainage of fluid, with the last side hole inserted 2 or 3 mm into the chest to ensure dependent drainage. Prior to insertion, the approximate length of the tube that should lie within the thoracic cage is estimated, and the position where the tube should emerge from the chest wall is marked with a silk tie.

Once the tube is properly placed in the pleural space it is fastened to the skin with 1-0 or 2-0 silk sutures, using a mattress stitch. Before fixing the tube, ensure that the last side hole is in the pleural space. The ends of the suture are not cut, but are wrapped around the tube, and secured with a tape so that they can be used later to close the wound after the tube is removed.

Throughout the procedure the proximal end of the tube is kept clamped and is opened only when the tube is finally connected to the drainage system. The placement is confirmed by the drainage of fluid, or by the bubbling of air in the drainage bottle.

Precautions

There is no absolute contraindication for inserting a chest tube. Coagulation abnormalities however should be corrected before insertion of the tube; in case of emergency, fresh frozen plasma or platelet transfusions may be given during the procedure.

A chest tube should never be inserted at the bedside for the purpose of draining a massive hemothorax. Accumulated blood in a massive hemothorax acts as a seal preventing further bleeding from the source, and insertion of a chest tube may precipitate catastrophic hemorrhage. Hence, a massive hemothorax should always be drained in the operation theater where facilities for controlling such a bleed, if necessary with an open thoracotomy, are available.

Complications

Common complications of chest tube drainage include improper positioning of the chest tube, inadequate drainage, bleeding, nerve damage, injury to the diaphragm, infection, surgical emphysema, and problems in the drainage system. Use of the correct technique of insertion and placement, and proper chest tube management whilst the tube is in place, will go a long way in preventing most of these complications.

Incessant pain may occur after re-expansion of the lung and may evoke a vasovagal response manifesting as bradycardia or hypotension. Intercostal nerve blocks or intrapleural lidocaine may help; parenteral analgesics may be needed if pain persists. Strong sedatives should however be avoided. Another major complication is re-expansion pulmonary edema following rapid evacuation of a large, long-standing pleural collection. Symptoms usually occur within 6 hours after rapid drainage. This complication can be avoided by slow evacuation of large collections.

After Care of Chest Tube Drainage

1. The bottle should never be raised above the chest level, as fluid may drain back into the pleural space and lead to infection, or cause a drowning disaster in the presence of a bronchopleural fistula. However, if the kind of drainage system demonstrated in Figure 7 is used, this complication can be avoided, because the draining tube never comes in contact with the water in the bottle.
2. The fluid level in the tube should oscillate with each breath. Failure to oscillate may be due to blockage or a kink in the chest tube, or may be due to full expansion of the lung.
3. The intercostal tubes should always be clamped whilst changing the bottles.
4. The original level of water in the bottle should always be marked, so that hourly drainage can be measured.
5. Very high negative suction via a suction pump should be avoided. Ideally, a suction control bottle should be added to the drainage system as a safety measure, as described earlier.

Chest Tube Removal

Chest tubes should be removed when there is minimal drainage (<100 mL/24 hours), and the chest X-ray shows complete re-expansion of the lung after clamping the outside tube for 24 hours. Check X-rays of the chest should be repeated after removal of the tube. Appearance of a small pneumothorax or minimal surgical emphysema is common, and often resolves by itself.

PERICARDIOCENTESIS[12]

Pericardiocentesis carried a high risk of morbidity in the past when done as a blind procedure. However, in the last decade the incidence of complications has decreased dramatically, largely due to improved imaging and monitoring techniques. However, bedside imaging facilities are not always available, and hence each and every resident doctor working in the ICU or emergency department of a hospital, should be familiar with the technique of blind pericardiocentesis, as this is the procedure of choice in the face of a life-threatening emergency like cardiac tamponade. Cardiac tamponade occurs when increasing accumulation of pericardial fluid produces cardiac chamber compression limiting ventricular filling, and significantly compromising the stroke volume. In such a situation, blind pericardiocentesis is justified as any delay in pericardial drainage may prove fatal.

Technique of Blind Pericardiocentesis (Fig. 8)

This procedure should always be performed in an intensive care setting with continuous ECG monitoring. The three approaches to the pericardium are subxiphoid, apical and parasternal.

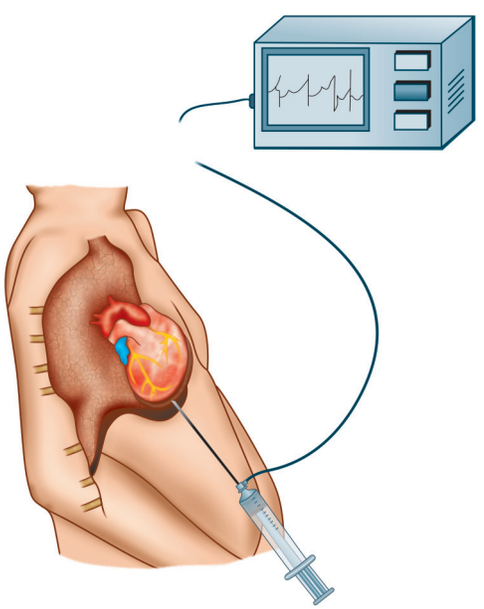


Fig. 8: Technique of blind pericardiocentesis

The *subxiphoid approach* is probably the safest as it avoids the pleura, the coronary and internal mammary arteries. The patient should be premedicated with atropine, and placed in an upright or semi-reclining position, as this allows pooling of blood inferiorly and anteriorly in the pericardial sac.

An area just left of the xiphoid tip is prepared and infiltrated with a local anesthetic. A 16–20 gauge spinal or cardiac needle attached to a syringe filled with local anesthetic is used, and the hub of the needle is connected to the V lead of an ECG via an alligator clip. The needle tip is introduced between the xiphoid and the left costal margin, so that it passes under the inner aspect of the rib cage, and the needle is then slowly advanced, with the tip pointing toward the left shoulder.

Whilst advancing the needle, a gentle suction is continuously applied to the syringe, and periodically small amounts of local anesthetic are injected. This helps to keep the needle patent, and also anesthetizes the deeper tissues. A resistance is felt on penetrating the diaphragm and pericardium. If a current of injury pattern, with ST-segment elevation, is recorded on the V lead tracing of the ECG (signifying the needle has touched the epicardium), the needle should be withdrawn slightly and readvanced in a more medial direction. Once fluid is aspirated, a soft catheter should be inserted with the help of a guidewire, and the needle withdrawn.

The apical approach is from the fourth or fifth intercostal space, 2 cm medial to the outer edge of the cardiac dullness, perpendicular to the chest wall. The needle bore is aimed at the right sternoclavicular joint. There is minimal risk of injuring the coronary arteries with this approach as there are no large vessels near the apex of the heart; however, the risk of ventricular or pulmonary lacerations are greater with this method.

The parasternal route lies 2 cm lateral to the sternum in the fifth intercostal space. The greatest danger of this approach is injury to the internal mammary artery, and hence this method carries a significantly greater morbidity than the two other approaches described earlier.

INTRA-AORTIC BALLOON PUMP[13]

Intra-aortic balloon pump (IABP) is the only accepted method of mechanical circulatory assistance available at present. It is now being increasingly used for sustaining patients with potentially reversible cardiac problems affecting the pumping function of the LV, when pharmacological therapy has failed to restore adequate coronary artery and systemic perfusion. The goal of balloon assistance is to provide temporary support to the LV when corrective surgery is planned in the near future, or spontaneous ventricular recovery is anticipated.

Intra-aortic balloon pump works on the principle that a balloon catheter inserted in the thoracic aorta inflates during diastole, and deflates during systole. The inflation improves diastolic-dependent coronary perfusion and myocardial

oxygen consumption, whereas the sudden deflation occurring in systole decreases the aortic end-diastolic pressure and lessens the workload on the LV, thereby decreasing the myocardial oxygen demand. Common indications for the use of IABP are—

- Immediate postoperative support after CABG surgery or other open heart surgery.
- Inpatients with unstable angina or impending infarction who are refractory to medical therapy and are awaiting bypass surgery.
- In acute myocardial infarction with cardiogenic shock.
- In patients with mechanical complications of acute myocardial infarction, which warrant surgical intervention, e.g. acute ventricular septal rupture, papillary muscle dysfunction or rupture.
- In patients with high risk for PTCA.
- In hemodynamically unstable patients who are awaiting surgery after a failed angioplasty.

Absolute contraindications for the use of IABP are dissecting aortic aneurysms, aortic regurgitation, irreversible brain damage and end-stage heart disease.

Equipment and Procedure

The two basic equipments required for this procedure are: (1) a drive unit and (2) intra-aortic balloon catheters. The operation of a drive unit is based on recognition of the variability of the interval between the electrical and mechanical events of the cardiac cycle. Hence, the precise timing of both inflation and deflation in relation to the events of the cardiac cycle becomes the most important function of the drive unit. The large-bore catheter has a 30 cm long polyurethane balloon wrapped tightly around its intra-aortic end, and has two concentric lumens running through its length. The central lumen leads to the catheter tip allowing a J tip safety guidewire that helps to introduce the balloon. This central lumen also allows recording of critical arterial pressure in the proximity of the balloon tip, thus eliminating the need of a separate arterial pressure line to obtain waveforms required for balloon pump timing. Concentric to the central lumen is the helium channel, through which the balloon is inflated with helium to a capacity of 30–40 mL.

Before selecting the groin through which the balloon catheter is to inserted, all the pulses in both lower extremities are compared and graded, and the leg with the greater pulse velocity is selected. A Swan-Ganz thermodilution catheter, and an intra-arterial line to record arterial waveforms, should also be inserted. However, separate arterial lines may not be necessary in most catheters, which allow intra-aortic waveform recording through their central lumen. The entire balloon device is inserted into the femoral artery at the groin, either percutaneously or by performing an arteriotomy. The balloon is then advanced up the aorta until the tip lies 1 cm below the origin of the left subclavian artery. Fluoroscopic guidance should be used whenever available, as it assures more precise placement.

Complications

The most commonly encountered complications in order of frequency are vascular (limb ischemia), infections, failure to place the balloon catheter, and bleeding.

Weaning

The balloon assistance should be withdrawn gradually by either decreasing the frequency of balloon inflations per cardiac cycle, or by stepwise reduction in the volume of the balloon. Weaning can usually be completed within 60 minutes provided the patient remains hemodynamically stable. If the patient's condition deteriorates, full volume IABP is resumed, and weaning may be reattempted after 6–24 hours.

INTRACRANIAL PRESSURE MONITORING

(Also see Raised Intracranial Pressure of Chapter Neurological Problems).

Indications[14]

Traumatic brain injury if Glasgow Coma Score less than 8 (after resuscitation). In addition, there should be evidence of an abnormal CT scan or in case the CT scan is normal, two or more of the following should be present—(a) age greater than 40 years; (b) unilateral or bilateral posturing; (c) systolic blood pressure greater than 90 mm Hg.

In patients with metabolic and other causes known to cause elevated intracranial pressure, such as subarachnoid hemorrhage, stroke, intracranial mass, hydrocephalus, hepatic encephalopathy and coma, poisonings.

Methods

Intracranial pressure (ICP) monitoring can be done by three methods—

1. Ventriculostomy with intraventricular catheter (IVC).
2. Subarachnoid catheter.
3. Subdural bolt.

Ventriculostomy

In this technique, an IVC can be placed through a craniostomy in the operation theater, or by a twist-drill ventriculostomy in the OT or in the ICU. The most preferred side is the posterior frontal lobe of the non-dominant hemisphere, and the catheter is passed through the brain to a depth of 6–8 cm. On finding CSF, the IVC is attached to a three-way stopcock that leads to a pressure transducer through one port and an external drainage system through another. The pressure transducer is connected to a monitor, which provides continuous digital and waveform display of the ICP.

The ICP baseline gently dips up and down with respiratory or ventilatory excursions. Zeroing of the pressure transducer should be done at the level of the external auditory meatus.

The IVC is the most accurate method of measuring ICP.[15] It can also be safely used to slowly drain CSF from the ventricles. However, it is difficult to perform in cases of head trauma as the ventricles are shrunken in size and the catheter is then left in the brain parenchyma. The main disadvantage is that it is more invasive and there are increased chances of infection. Most units use prophylactic antibiotics when IVCs are used.

Subarachnoid Catheters

A subdural catheter can be inserted into the subarachnoid space inside the skull by the same technique described for IVCs. This method can be used to monitor the ICP but not for drainage of CSF.

For one-time measurement of ICP, a catheter into the subarachnoid space in the L3–L4 space can be used, provided obstructive hydrocephalus has been ruled out by imaging techniques. However, CSF cannot be drained by this method.

Subdural Bolt

In this technique, a hollow self-tapping bolt is inserted into a burr hole in the skull at the bedside, and the dura at the base of the bolt is perforated with a spinal needle, so that CSF fills the bolt. Pressure tubing filled with saline is then connected to the bolt and communication with an external transducer is established.

This technique is used when the first two techniques are difficult. Also, this method is associated with a lower infection rate as compared to ventriculostomy. However, this method cannot be used for drainage of CSF.

Fiberoptic ICP monitors, which use miniature transducers incorporated into their ends can also be used to measure ICP.

Several parameters, such as cerebral blood flow velocity (CBFV) in different parts of the brain circulation, measured through the use of transcranial Doppler, have been suggested for estimating the ICP noninvasively.[16] However, as yet, none of these methods are reliable enough to substitute for invasive ICP monitoring.

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CHAPTER 7

Cardiac Monitoring in Adults

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GENERAL CONSIDERATIONS

The most important aspect of cardiac monitoring is frequent clinical assessment, which includes physical examination and intelligent observation. Proper evaluation of important symptoms, such as chest pain, dyspnea, cough and monitoring of vital signs, is of prime diagnostic value in emergency situations. Accurate inspection of the jugular veins in the neck can give a good idea of the central venous pressure (CVP) in the absence of a central venous catheter. This clinical observation should also be used frequently to countercheck the reliability of any invasive CVP measurement. Repeated chest auscultation is essential to rule out signs of early pulmonary edema. Monitoring of urine output is imperative for the assessment of renal perfusion. Relevant blood tests and routine chest X-rays though essential aspects of cardiac monitoring are beyond the scope of this chapter, which focuses mainly on monitoring techniques, which involve instrumentation. These include: (i) ECG monitoring; (ii) invasive hemodynamic monitoring; (iii) noninvasive or minimally invasive methods of hemodynamic monitoring using various modalities; (iv) assessment of volume responsiveness; (v) discussion on hemodynamic variables, pulse wave analysis and their clinical applications.

ECG MONITORING[1]

Bedside detection of cardiac arrhythmias, and of ST segment changes to some extent, are the most important objectives of continuous ECG monitoring. There are certain technical details to be observed for skin preparation and electrode placement in order to ensure the accuracy and the optimal benefit from the graphic information. Shaving and careful skin preparation to achieve proper electrode contact is essential. Further, electrodes should be so placed that they do not interfere with physical examination, the recording of a 12-lead ECG, or the use of a defibrillator. Electrode wires should always be checked for breaks or fractures, as this may result in artifacts.

Selection of the Monitoring Leads

With the advent of complicated cardiac surgeries, invasive interventions, such as angioplasties, electrophysiological studies and implantation of technologically advanced pacemakers; the goals of ECG monitoring have expanded beyond the simple heart rate and basic rhythm to the detection and diagnosis of various complex arrhythmias. The standard 12-lead ECG is not practical for continuous patient monitoring. Hence, electrode placements at alternative sites are used. These offer various advantages such as: (i) minimizing the number of electrodes; (ii) wider chest space available for auscultation and defibrillation; (iii) improved detection of certain complex arrhythmias, ST segment shifts and correct measurements of QT intervals.

The current monitors provide 3-lead or 5-lead trunk cables but the *EASI*[2] lead configuration used by many workers is an alternative to the commonly used 5-electrode or the Mason-Likar lead monitoring system. The EASI system enables continuous 12-lead ECG monitoring using only five electrodes (four recording electrodes and one grounding electrode). In this EASI system, the E lead is placed in the inferior most aspect of the sternum. A and I are placed on the left and right mid-axillary line respectively and S is placed on the sternum manubrium. The 5th lead, which is the grounding electrode can be placed anywhere on the torso. The cable trunk has a

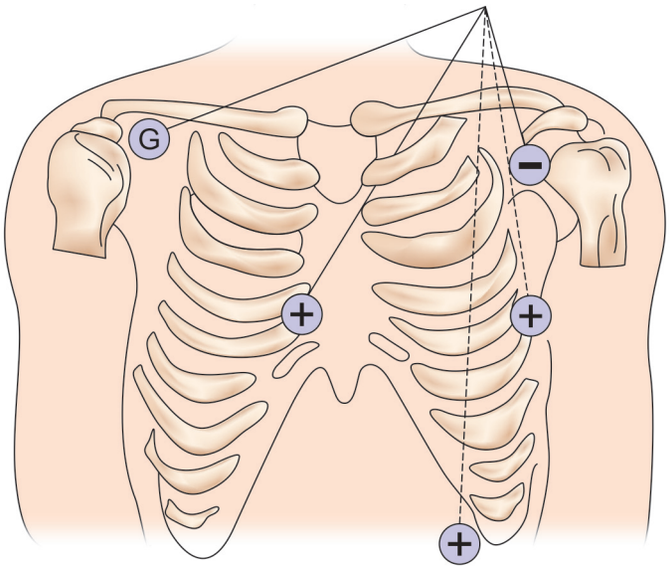

Fig. 1: MCL_1 hook-up shown by uninterrupted lines representing positive, negative and ground electrodes. MCL_6 and M_3 are obtained by simply changing the positive electrode from the V_1 position to the two positions as shown by broken lines, leaving the negative and ground electrodes undisturbed

color coding of the individual electrodes. In comparison with the 12-lead electrodes, there was 100% agreement for rhythm identification; however, because of the differing amplitudes between the EASI and standard ECG systems, chamber size did not compare well. The major advantages of this system are the easy and rapid application of the leads, with improved patient comfort and least waveform interference and it also has excellent reproducibility for serial comparisons.

Further, innovations have been tried with some special lead configurations. The modified CL_1 (MCL_1) hook-up (Fig. 1) has been the most popular lead used for monitoring since many years and is a simple, excellent alternative, which gives similar information to V_1. The V_1 or MCL_1 lead is excellent for studying atrial activity by displaying well formed P waves and also for the study of QRS complexes. Here the positive electrode is placed at the V_1 position, the negative electrode at the left shoulder, and the ground electrode may be placed at any site, but is usually placed at the right shoulder. As seen in Figure 1, this leaves sufficient space over the precordium for physical examination and for emergency cardioversion. In addition, since it closely resembles V_1, this lead offers several diagnostic advantages—

- It displays well-formed P waves.
- It is easy to distinguish between left bundle branch block (LBBB) and right bundle branch block (RBBB).
- It is the best lead for distinguishing between a ventricular ectopic originating from the left ventricle (LV) with a positive QRS deflection, and one originating from the right ventricle with a negative QRS deflection.

More information can be provided by using a left chest lead MCL_6 (which simulates V_6), or M_3 (modified lead III). This can be easily done without disconnecting the entire MCL_1 hook-up as shown in the Figure 1. Lead V_6 or MCL_6 is an important lead for differentiating between aberration and ectopy whenever V_1 fails to reveal this. A sinus beat in V_6 always begins with a small q wave; disappearance of this q wave with onset of tachycardia, is characteristic of left ventricular tachycardia rather than sinus tachycardia with aberrance. V_6 or MCL_6 is also very useful in monitoring ischemic ST segment changes, especially in patients with unstable angina, as this lead represents the main left ventricular free wall.

In rare instances when one wants to demonstrate the polarity of the P wave, M_3 (which simulates Lead III), will have to be used. For instance a retrograde P wave will show up clearly in M_3 in case of a junctional rhythm, whereas both sinus and retrograde P waves are predominantly positive in MCL_1.

This easy method of changing leads comes handy in monitoring pacemaker patients, as one lead may not show a pacemaker artifact; however, on changing the lead configuration, this will become clearly evident. This is more useful during bipolar pacing, where the pacemaker spikes or artifacts are not as prominent as in unipolar pacing.

As recognition of the P wave is the key to diagnosis of arrhythmias in bedside monitoring, all efforts should be made to magnify the P wave so as to render it easily recognizable. Certain invasive methods, such as inserting intra-atrial electrode catheters or *esophageal electrodes*, can greatly enhance the P wave, which may have been virtually indiscernible with surface leads. However, these forms of monitoring may not be feasible, particularly in very sick patients, and another noninvasive special lead, viz. S_5 should be tried. This was first introduced by French cardiologists, and is easily obtained by placing the positive electrode in the fifth intercostal space close to the sternum (just below V_1 position), and the negative electrode on the manubrium of the sternum. This lead may sometimes succeed in magnifying the P wave, and if so, it is preferable to invasive means of monitoring.

At times, it would be interesting to study lead *aVR* or any other lead which shows the smallest ventricular complex as elusive P waves or small pacemaker spikes are often more prominently seen in these leads, provided there is minimum baseline disturbance.

ECG Monitoring in Pacemaker Implanted Patients

Pacemaker malfunction of temporary pacing and of the basic single chamber implanted pacemaker have been described in the previous chapter. However, present day devices, like AV synchronous or biventricular pacemakers, need various lead configurations to decipher the small pacing spikes and waveform configurations for detailed analysis. Often a 12-lead ECG may have to be taken frequently for this purpose.

Unlike in ventricular pacing where pacemaker spike precedes the QRS complex which has an LBBB configuration, in atrial pacing, it precedes the P wave and the P wave morphology may change depending on the location of the atrial lead but the PR interval and the configuration of the QRS complex are independent of the atrial pacemaker and are determined by the intrinsic characteristics of the patients

conduction system. Fusion beats show a QRS morphology that is in between the native and paced QRS complex. A pseudofusion is shown by a pacing spike appearing just after the beginning of a native QRS complex giving the appearance of a pacing capture. However, here, as the pacing stimulus is delivered during the refractory period, it does not capture the heart.

In AV sequential pacing, the pacemaker spikes are seen before the P wave and QRS complex. If, however, the inherent atrial rate is faster than the programmed lower rate of the pacemaker, there will be no pacing spike seen prior to the P wave as the P wave originates from the sinus node or from an ectopic atrial focus. The QRS morphology will however depend on the programming of the pacemaker device and atrioventricular conduction and may represent either a paced QRS morphology or a morphology of a normal beat.

In biventricular pacing also known as cardiac resynchronization therapy (CRT) the pacing leads are placed in the right atrium, right ventricle and coronary sinus (pacing the LV). Hence, the QRS complex will show an indeterminate bundle branch block morphology or could even be narrow in configuration.

Pacemaker malfunction due to loss of captures is recognized on the ECG by absence of P wave or a QRS complex following a pacemaker spike. Non-capture could be intermittent or persistent. Pacemaker malfunction can also occur due to undersensing or oversensing of intrinsic cardiac activity. In undersensing where the pacemaker fails to sense the native electrical signal there will be a pacing spike with or without a capture depending on the refractoriness of the tissue and which will have no relation to the underlying cardiac activity. Oversensing usually occurs with unipolar leads when pacemaker senses far field external signals not arising from the representative cardiac chamber. In oversensing, the device inhibits pacing resulting in asystole unless there is an intrinsic cardiac activity. This can occur due to electromagnetic interference such as from electrocautery or interference from electrical myopotentials produced from the diaphragm or pectoral muscles.

HEMODYNAMIC MONITORING

Hemodynamic monitoring is in essence an invasive method of monitoring arterial, central venous and pulmonary artery pressures (PAPs). Measurement of cardiac output (CO) and saturation of oxygen in mixed venous blood ($S\bar{v}O_2$) are other important aspects of hemodynamic monitoring. With the information gained from the above parameters, one can calculate the ventricular work load, vascular resistances, oxygen transport (DO_2), and oxygen consumption ($\dot{V}O_2$); this data can be extremely useful in the management of critically ill patients. However, mere numerical values are of limited value, and a balanced clinical approach in the interpretation and application of these values cannot be overemphasized. Further, as doctors caring for seriously ill patients, we witness life at its most poignant, intimate and critical moments. It is thus obligatory, that we learn to use these invasive techniques with sensitivity and skill.

There are varied indications for hemodynamic monitoring which will be discussed under the appropriate procedures. Traditionally, hemodynamic monitoring is synonymous with pulmonary artery catheterization and thermodilution method of measuring CO which, however, remains the gold standard against which other methods are validated.[3] Today with the advent of new technology less invasive methods are available which are also capable of measuring continuous CO beat by beat, using several pulse contour devices. However, the fundamental goal of monitoring remains constant—the early detection, and the prompt restoration to normal of inadequate perfusion. Various invasive and minimally invasive monitoring systems available are highlighted in Table 1.

PRESSURE MONITORING SYSTEM

The equipment required for direct pressure monitoring consists of three main components: (1) the transducer, (2) pressure lines and (3) the pressure monitor (Fig. 2).

A transducer is a device that converts the mechanical energy created by the arterial or venous pressure waves into electrical energy, which in turn gets displayed on the monitor as a waveform. Most transducers available are strain gauge devices or quartz transducers. Quartz transducers are more frequently used today as they are conveniently designed, more durable, and less affected by ambient conditions. The latest in transducer technology are the disposable or single-use units, and most of these are modifications of strain gauge devices.[4]

Pressure lines include the tubings, connecting stopcocks, the pressure infusor bag and a continuous flush valve device also commonly known as intraflo.

The pressure infusor bag is a hollow pressure bag wrapped around a heparinized saline intravenous bag, which can be inflated to high pressures. Intraflo is a flushing device, which under constant pressure (around 300 mm Hg) assures a continuous flow of heparinized solution at a rate of 3 mL/hour through the system. This prevents clotting and backflow, and also provides for the manual flushing of the fluid column as and when necessary.

The pressure monitor is an amplifier system which can display waveforms and digital readouts on a screen, in addition to having recording facilities. With improving technology, the bedside pressure monitors available today are highly sophisticated, significantly smaller in size and extremely reliable. Even so, monitors may not always be 100% accurate; in fact, one recent study has shown that errors of 5–10 mm Hg are frequent, and gross errors of 30–40 mm Hg are not uncommon. In order to minimize such errors and obtain accurate pressure data, the ICU personnel must familiarize themselves with the equipment, and be able to set up the system with accuracy and speed; they should also be competent in detecting and solving problems encountered during monitoring.

Table 1: An overview of hemodynamic monitoring modalities

Modality	*Device*	*Features and requirements*	*Variables monitored and derived*
Invasive—			
• Pulmonary artery catheterization and thermodilution technique	Edwards Lifesciences	PAC and thermodilution catheter, specific transducer and pressure plus CO monitor	CO, PCWP, CVP, RAP, RVP, PAP, SVR, PVR, SV, LV-SW, RV-SW, DO_2, $S\dot{v}O_2$, O_2ER
Less invasive, minimally invasive and noninvasive—			
• CVP	Edward Lifesciences, Arrow, etc.	Seldinger introduction set	CVP
• MvO_2	Edward Lifesciences	Continuous CO monitor and PAC	CCO, MvO_2
• $S\dot{c}VO_2$	Edward Lifesciences	Continuous CO monitor and CVP line	CCO, $S\dot{c}VO_2$
Pulse pressure analysis—			
• Calibrated	PiCCOplus	Thermistor-tipped arterial cath and CV line	CCO, SVV, CVP, PPV, GEDV, EVLW
	LiDCOplus	Lithium dilution set and arterial cath and CV line	CCO, SVV, PPV, CVP
	EV1000/Volume view	Thermistor-tipped arterial cath and CV line	CCO, SVV, CVP, GEDV, EVLW
• Uncalibrated	LiDCOrapid	Arterial cath	CCO, SVV, PPV
	FloTrac/Vigileo	Arterial cath	CCO, SVV
• Noninvasive	Nexfin	Finger pressure cuff	CCO, SVV, PPV
Doppler—			
• TOE	CardioQ/CardioQ-ODM (Deltex medical)	Esophageal probe	CCO
• TTE	USCOM (Australia)	Transthoracic probe	CO(I)
Applied fick principle—			
• Partial CO_2 rebreathing	NICO (Novametrix)	Rebreathing loop	CO every 3 min.
• Dye dilution	DDG analyzer (Nihon Kohden)	Specific cauteneous sensor	CO(I)
Bioimpedance/bioreactance—			
• Endotracheal bioimpedance	ECOM (Conmed corp)	Specific endotracheal tube and arterial cath	CCO
• Thoracic/whole body impedance	BioZ (Cardio dynamics)	Specific electrodes	CCO
• Thoracic bioreactance	NICOM (Cheetah med)	Specific electrodes	CCO, SVV
• Plethysmographic variability (noninvasive)	MASSIMO	Specific transcutaneous probe	PVI

Abbreviations: CO, cardiac output; CO(I), intermittent CO; CCO, continuous CO; CVP, central venous pressure; RAP, right atrial pressure; RVP, right ventricular pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; SV, stroke volume; LVSW, left ventricular stroke wall; DO_2, O_2 delivery; MvO_2, mixed venous SaO_2; $S\dot{c}VO_2$, central venous SaO_2; O_2ER, oxygen extraction ratio; PPV, pulse pressure variation; SVV, stroke volume variation; GEDV, global and diastolic volume; EVLW, extra vascular lung water; PVI, plethymographic variation index; TOE, transesophageal; TTE, transthoracic echo; SvO_2, saturation of mixed venous oxygen.

Assembly and Calibration of the Monitoring System

The pressure monitoring system is assembled as shown in Figure 2. Care should be taken to remove all air bubbles from the tubings and the dome of the diaphragm whilst setting up the pressure lines. The extension tube connecting the intraflo to the catheter should be a stiff, non-distensible pressure tubing of approximately 100 cm length. Once the system is connected and ready for monitoring, it should be balanced, calibrated and placed at the correct reference point.

Reference point There is always a hydrostatic pressure gradient in a fluid-filled system, consisting of blood in the vessels interfaced with a column of saline in the catheter, tubings and transducer. For instance, if the transducer is manually raised or lowered, there are bound to be changes

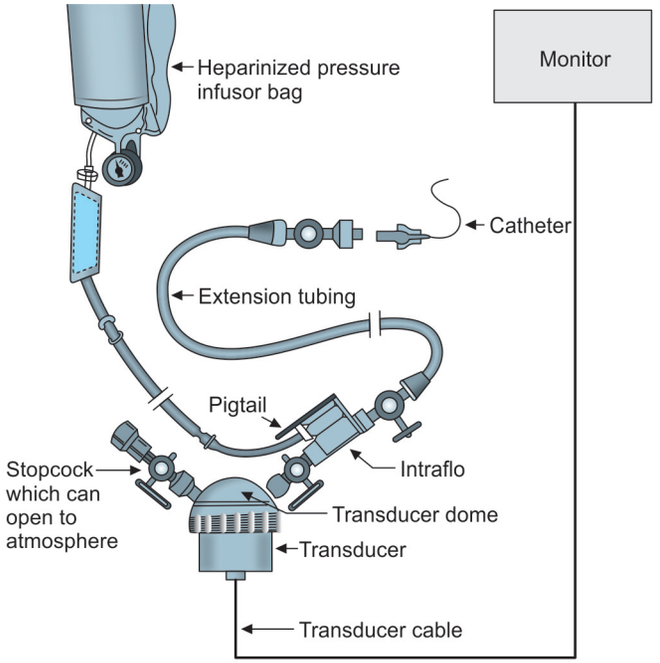

Fig. 2: Assembly of the pressure monitoring system

in pressure recordings, proportional to the weight of the fluid column applied to the transducer diaphragm. In order to eliminate this undesired pressure head, the transducer diaphragm and the catheter tip, which are considered as two ends of the pressure line, should always remain exactly at the same level. By convention, we relate central hemodynamic pressures to the level of the heart, or more specifically to the mid left atrium (LA), at which level the catheter tip is supposed to lie. For a patient in the supine position, the mid-chest level is accepted as a reference line approximating the left atrial level. However, whilst nursing patients in semi-upright positions, an exact point of reference becomes necessary. This is represented by a point on the mid-axillary line at the level of the fourth intercostal space. Before beginning zero referencing procedures, the transducer must be placed at this appropriate reference point, called the zero reference point. This is the accepted reference point for measurement of PAPs and CVP monitoring; however, in case of arterial monitoring the transducer should be at the level of the cannulated artery, which should also be at the heart level.

The exact procedure for zero referencing or balancing is shown in Box 1. The transducer calibration procedure tests the transducer by exposing it to a known pressure (Hg manometer), unlike zero referencing, which balances the transducer output with the atmospheric pressure.

Eliciting of a waveform response (Fig. 3) is another rapid bedside method of checking the integrity of the monitoring system. Normally on pulling and releasing the pigtail of the intraflo, the waveform on the monitor shows a rapid rise with an equally rapid return to a point below the baseline (undershoot), followed by a short period of oscillations. If this return to the baseline is slow with inadequate oscillations,

Box 1: Zero referencing procedure

- Place the transducer dome at the level of the zero reference point
- Adjust the two transducer stopcocks so that one is open to the atmosphere, and the other closed toward the patient
- The digital readout and oscilloscope display on the screen should now both read 0 mm Hg
- If they do not, follow the particular machine instructions so as to achieve a zero balance
- Once properly zeroed, close the stopcock which is exposed to the atmosphere, and open the line to the patient. The waveform that follows is now ready for interpretation

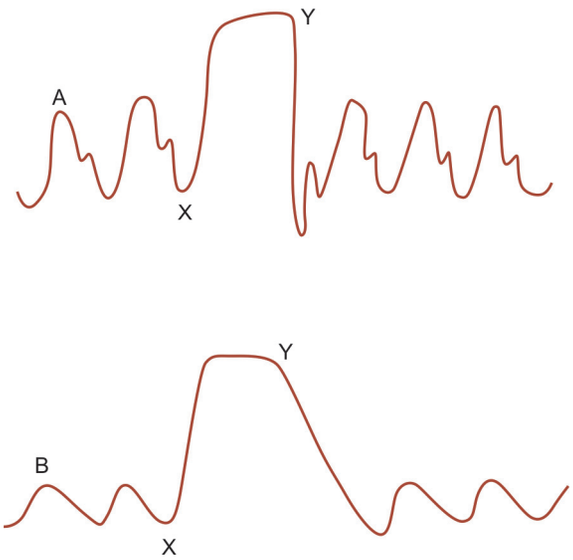

Fig. 3: Eliciting a waveform response at the bedside
A = normal waveform response
B = dampened waveform response
X = intraflo activated by pulling the pigtail
Y = release of pigtail

it suggests some sort of occlusion in the tubing or catheter, which needs to be looked into.

Common Problems Related to Monitoring Systems

Distortion of the waveform, questionable pressure readouts, and artifacts are three common problems encountered whilst dealing with pressure monitoring systems, irrespective of venous or arterial catheterizations. Table 2 enumerates the causes, and gives guidelines for solving most of these problems. Some general precautions, which need to be taken for smooth and uncomplicated monitoring are listed in Box 2.

ARTERIAL PRESSURE MONITORING[5]

The techniques and complications of arterial cannulation are described in the Chapter Procedures in the Intensive Care Unit.

Arterial pressure monitoring is initiated in all patients with compromised hemodynamic status. In these cases, the cuff

Table 2: Trouble-shooting guide for pressure monitoring systems

Problems	*Check and correct*
Waveform related problems—	
No Waveform	Power supply, calibration and balancing, loose connections, clots in the tubings, stopcock direction, broken catheter, catheter tip abutting against the vessel wall
Over-dampened waveforms	Air bubbles in the pressure lines, kinks or clots in the tubings, catheter tip abutting against the vessel wall
Questionable pressure readings	Balancing and calibration, reference level of transducer, loose connections in the pressure lines, faulty intraflo
Artefacts	Patient movements, respiratory movements, electrical interference, catheter whip artifact

Box 2: General precautions and care of pressure lines during monitoring

- Employ aseptic technique at all times
- Select uncomplicated monitoring kits (avoid long pressure lines or too many interconnecting tubes, in order to eliminate kinks, leaks and air bubbles)
- Once system is in use, avoid disconnecting the line for any reason
- Avoid blood collection and administration of IV drugs through these catheters
- Avoid use of sharp instruments when removing dressings around the catheter site
- Do zero referencing at the beginning of the procedure, and each time following interruption of continuous monitoring, whatever the reason. In any case, it is recommended that zero referencing be done 3–4 times a day

method of recording blood pressure is likely to be inaccurate as Korotkoff's sounds are less audible at low flow rates. It is also indicated in severely vasoconstricted patients, and in patients being treated with vasoactive or antihypertensive drugs, which require careful titration of dosage to avoid precipitous changes in arterial blood pressure.

The radial artery is usually the preferred site for placement of an arterial catheter, provided that the adequacy of collaterals to the ulnar artery has been assessed and determined to be sufficient by the Allen's test (see Chapter Procedures in the Intensive Care Unit). In addition to the fact that the hand receives a generous collateral circulation, the radial artery is superficial, compressible and easily accessible. Cannulation of the artery involves little or no risk to neighboring anatomical structures, and above all the surrounding skin area can be easily kept clean. The only drawback of the radial artery is its relatively small size which may limit the success of cannulation. For proper monitoring the placement catheter should be inserted right up to the hub to avoid kinking, and the wrist should be maintained in a neutral position.

The brachial, axillary and femoral arteries are other possible sites for cannulation, but they should never be the first choice for arterial catheterization as they have many disadvantages, and more serious complications may ensue.

During intra-arterial monitoring, the catheter should be properly secured to avoid accidental disconnection resulting in significant blood loss. Silent bleeds or oozing within the tissue spaces, which are most common following femoral punctures, may lead to huge hematomas. Aseptic measures should be strictly followed during catheterization, subsequent manipulation and blood sampling.

The extremity distal to the catheter site should be frequently assessed for adequacy of blood flow, and neurological integrity. The pressure infusor bag should always be pumped to a level higher than the systolic pressure so as to prevent reverse blood flow in the catheter, and prevent embolization at a peripheral site.

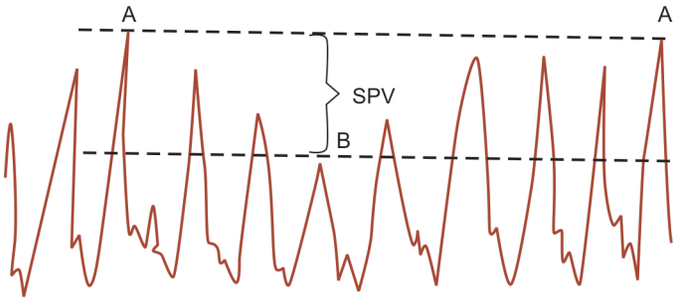

Fig. 4: Systolic pressure variation. **A** is the maximum systolic pressure and **B** is the minimum systolic pressure during one ventilatory cycle (A-A')

Waveform Interpretation and Clinical Applications (Fig. 4)

The normal arterial pressure produces a characteristic waveform, which has two main components. The initial upstroke (anacrotic limb) represents the rapid ejection of blood from the ventricle through the open aortic valve, the peak value representing the systolic pressure. This is followed by the downward trend (dicrotic limb) as the pressure begins to fall. This fall in pressure continues till it reaches a point where the pressure in the ventricle is less than the pressure in the aortic root; the aortic valve closes at this point, producing a characteristic dicrotic notch in the descending limb of the waveform. The closure of the aortic valve signals the onset of diastole, which progresses till it reaches its lowest resting level. The value at this level represents the diastolic pressure.

The configuration of the waveform and the actual pressure measurements vary depending on the catheterization site. Arteries more distal from the aorta show higher systolic and lower diastolic pressures; hence, systolic and diastolic pressures in the peripheral arteries may not be an accurate reflection of the pressure in the aorta. However, the mean pressure remains relatively constant irrespective of the anatomical site of catheterization, and it is this value which is most commonly used to derive various hemodynamic parameters. The mean pressure is measured electronically

Table 3: Advantages and disadvantages of various central venous sites

Site	*Advantages*	*Disadvantages*
Subclavian	• Accessible and secure • Affords unrestricted patient movements • Easy to keep the area sterile and maintain intact dressing • Allows very rapid flow	• Likely complications— – Pneumothorax – Injury to subclavian artery – Hemothorax • Operator skill—advanced • Difficult to compress if bleeding occurs
Internal jugular	• Low risk of pneumothorax • Short and direct pathway to the RA • Unrestricted arm movement • Allows very rapid flow	• Likely complications— – Injury to common carotid artery or trachea – Operator skill—advanced; more difficult in patients with short neck – Restriction of neck movement – Landmarks not very clear
Femoral	• Operator skill-easier techniques with high success rate • Most useful for emergency pacing as it is fastest pathway to the RV apex	• Likely complications— – High infection rate – Ischemia of lower limb • Difficult to maintain a sterile intact dressing
Antecubital site	• No major complications	• Difficult to advance the catheter • Restricted arm movements • Thrombophlebitis

by dividing the area under the arterial waveform by the duration of the cardiac cycle. Mean pressure can also be estimated manually as the diastolic pressure and one-third the pulse pressure, but this estimate is often unreliable, and it is preferable to use the electronically derived measurement.

The size and configuration of the waveform can be altered due to abnormal physiological conditions such as severe hypertension, shock and aortic stenosis. Careful observation of the waveform are useful to the extent that they may roughly indicate changes in the hemodynamic status, depending on changes in an individual's waveforms over a period of time; however, mere interpretation of a waveform at a specific point in time cannot reflect on the patient's cardiovascular status, and may be most misleading. Interestingly, Parel and coworkers[6] had observed in their study in 1987 that significant systolic pressure variation (SPV) occurs during positive pressure ventilation which is discussed later in this chapter.

CENTRAL VENOUS PRESSURE MONITORING[7]

Central venous catheterization (see Chapter Procedures in the Intensive Care Unit) provides venous access to one of the central veins, and can be used to monitor the CVP. Various anatomical sites may be used to insert the catheter into the central vein. The advantages and disadvantages of the more commonly used sites are listed in Table 3. We find that the internal jugular and subclavian sites are ideally suited for long-term monitoring.

The actual measurement can be done by using a simple water manometer or attaching the central line to a transducer. *Water manometer technique* is a simple bedside procedure, which does not require any sophisticated equipment. The central venous catheter is connected to a three-way stopcock via an extension tubing which in turn is connected to a pre-calibrated manometer placed on a stand. The level of CVP is read by observing the descent of the fluid column in the manometer, which is in direct continuity with the blood in the central veins. The descent eventually stabilizes and the reading at this level is the CVP measurement (in cm of H_2O). Marked respiratory fluctuations in the fluid level are expected, and in fact, the patient is at times encouraged to cough or breathe deeply to confirm the catheter placement in a central vein. However, most ICUs today use a *transducer monitoring technique* whereby the proximal end of the CVP line is connected directly to a pressure transducer and a continuous digital recording and a waveform of RA pressure is obtained on the monitor.

Clinical Application

The mean pressure in the right atrium is 0–6 mm Hg (using a transducer monitoring system), and 3–8 cm of H_2O (when using a simple water manometer), the conversion being 1 mm Hg = 1.36 cm of H_2O. The CVP catheter may be placed in the superior vena cava instead of the RA because it accurately reflects the right atrial pressure and waveforms. Placing the catheter tip in the right atrial cavity may inadvertently cause the tip to negotiate the tricuspid valve and momentarily record the higher RV pressure; this may also result in ventricular premature contractions (VPCs). However, in the case of a pulmonary artery catheter (PAC), the proximal port would automatically lie in the RA.

The CVP or RA pressure reflects the right ventricular end-diastolic pressure (RVEDP). Ordinarily in healthy individuals the RVEDP and the left ventricular end-diastolic pressure (LVEDP) correlate rather well. Therefore, in a young person with normal cardiac function, the CVP correlates well with the LV filling pressure, and can be used as a guideline for

monitoring the LV preload during fluid therapy. However, in clinical practice, it is fallacious to assume that the CVP is a good guide to LV filling pressure in all cases; in fact, there may be a disparity between the right and left ventricular function in critically ill patients, for more than one reason. This disparity can occur in patients with isolated right ventricular dysfunction caused by tricuspid or pulmonary valve defects, right ventricular infarcts or pulmonary hypertension. In all these conditions, the CVP will be high, and will not correctly reflect the LV preload. It can also occur in patients with isolated LV dysfunction in which case the CVP will remain within normal limits and will not reflect the high LVEDP. Because of this frequent disparity between right and left ventricular functions in critically ill patients, CVP readings should be interpreted with circumspection.[8]

A CVP reading can be most misleading if it is interpreted as an isolated reading. In order to obtain maximum benefits, serial measurements over a period of time should be studied and correlated with the patient's clinical state. This is most important when considering fluid replacement in elderly patients suspected of having cardiac dysfunction. In such patients, small amounts of fluid challenge should be given whilst closely monitoring the rise in CVP. If there is a sharp rise, further fluid challenge should be withheld, or given very cautiously. Also, in such patients, a CVP value even in the lower limit of normal should be accepted as the endpoint, provided there is a significant clinical improvement in perfusion. If this is practised meticulously, CVP monitoring can be a safe alternative in the absence of a PAC.

There are several other limitations to the use of CVP, for instance, if the venous tone is increased in severe hypovolemia, the CVP may not fall in proportion to the fluid loss. Similarly patients on mechanical ventilator support may show falsely elevated CVP values due to raised intrathoracic pressure. Falsely raised CVP values may also occur with external compression of the vena cava because of a tumor mass, or due to increased intra-abdominal pressure.

PULMONARY ARTERY (PA) PRESSURE MONITORING[9-11]

As the LV is primarily responsible for the forward flow of blood perfusing the vital organs, it is logical to assume that an accurate means of measuring the LV function would be the most essential part of critical care monitoring. Though clinical findings such as tachypnea, moist lung sounds, or gallop rhythm are common manifestations of LV failure, unfortunately they are not sensitive indicators of rapidly deteriorating LV function. They may appear late in the natural history of the disease, and vital time may be lost before the hemodynamic disturbance is corrected.[10] Measurement of the LV filling pressure (or LVEDP) without actually entering the left side of the heart was first made possible by the discovery of a flow-directed PAC by Swan and Ganz in 1970. Here the catheter tip with an inflated balloon just proximal to it was floated far into one of the branches of the pulmonary artery and wedged, so that the catheter tip was in direct continuity with the LA via the pulmonary veins, and hence reflected the LA pressure which was the same as LVEDP, provided there was no LV inflow obstruction. In addition, the PAC could measure the RA pressure through its proximal lumen, and the CO could also be measured by the thermo-dilution technique. Further, mixed venous blood could be collected from the distal lumen of the catheter for assessment of $P\bar{v}O_2$ and saturation of mixed venous oxygen ($S\bar{v}O_2$).

Indications[11-13]

Though bedside monitoring with a balloon tip PAC has been in use since the last 30 years, controversy still persists regarding its value. However, in conditions such as septic shock or acute lung injury (ARDS), manipulation of certain hemodynamic parameters and of oxygen transport, have definitely changed the approach to therapy, with an improved outcome. There is also no dispute over the fact that constant monitoring of LV preload is mandatory whilst infusing large volumes of fluids or giving massive transfusions, especially in the elderly or in those with suspected cardiovascular dysfunction. Similarly, pulmonary wedge pressure measurements are helpful in differentiating between cardiogenic pulmonary edema and non-cardiogenic pulmonary edema.[14]

It is clear that PAC provides data that can be used to make therapeutic decisions as above. However, the critical question is whether these therapeutic decisions improve outcomes. Some studies have suggested that the use of PAC actually worsens outcome.[15] This rekindled the strong debate regarding the efficacy and safety of PAC. Dalen and Bone, in their editorial accompanying this study[16] recommended that the US (FDA) should issue a moratorium on the use of PAC till a designed randomized clinical trial of use of the PAC in critically ill patients is undertaken. However, a joint statement by the American College of Chest Physicians (ACCP) and the American Thoracic Society (ATS)[17] stated that there was no indication for the moratorium on the use of the PAC at that time, but released the following recommendations—

- Further prospective randomized controlled trials of the PA catheter.
- The decision to insert a PAC and its potential benefits should be weighed against the risks involved.
- Informed consent should be obtained whenever possible.
- Only physicians knowledgeable about the technique of proper placement, potential complications and interpretation of the data generated should use the PAC and proper documentation should be mandatory.

Recent studies have consistently shown that PAC monitoring has not demonstrated improved survival or reduced ICU or hospital length of stay compared with control groups. However, it remains plausible that there is a subgroup of patient population for whom PAC as a guide to hemodynamic management may be helpful. Though, in the final analysis, it is worth stressing that diagnostic tests and monitoring devices do not alter clinical outcome, but treatment does. If

Box 3: Indications for pulmonary artery pressure monitoring

- In critically ill, hemodynamically unstable patients—
  - Shock (of any etiology)
  - Burns, sepsis, peritonitis, acute renal failure, acute lung injury, fulminant tetanus, etc.
- In patients where the diagnosis is uncertain—
  - Cardiogenic versus non-cardiogenic pulmonary edema
  - Acute respiratory failure with uncertain cardiac status
  - Acute myocardial infarction with a new loud murmur indicating acute rupture of the interventricular septum, or of a papillary muscle
  - Suspected pulmonary embolism
  - In patients with acute myocardial infarction and shock, in whom hypovolemia has to be differentiated from pump failure
- As a therapeutic guideline under the following conditions—
  - Massive fluid replacement in patients with severe fluid loss, especially in elderly patients, or in those with a history of ischemic heart disease
  - Fluid management in patients with non-cardiogenic pulmonary edema (ARDS)
  - In acute hemorrhage necessitating massive transfusions, particularly in patients with associated cardiac or renal problems
  - Management of patients with shock, or other critically ill patients on inotropic and/or vasodilator drugs
  - In patients with pump failure who respond unsatisfactorily to initial therapy
- Patients at risk of hemodynamic decompensation—
  - Preoperative monitoring in all seriously ill patients (cardiac or non-cardiac surgery)
  - Patients with underlying cardiac disease on mechanical ventilator support with PEEP or continuous positive pressure

PAC does not alter treatment decisions, it can have no positive effect on the clinical outcome but may unnecessarily add to potential complications. Hence, to benefit patients, the PAC must provide information that is not otherwise available and the information so provided should be useful in selecting a treatment plan that has proven clinical benefit.[18] It should also be realized time is of essence; there are studies, which show significant improvement in outcomes, when therapy guided by PAC was given early, within 8–12 hours postoperatively.[19,20]

The general indications for PAP monitoring are listed in Box 3. These are only guidelines and there is no compulsion to adhere to them to the letter. Each individual patient should be carefully considered, and the anticipated benefits must clearly outweigh the possible risks.[21] By and large this procedure should not be used too liberally in developing countries, and its use should be restricted to centers having the proper set-up, expertise and an assured aseptic environment.

Catheter Design

A wide range of catheters (from the adult to the pediatric size) are available for various clinical applications. They range from

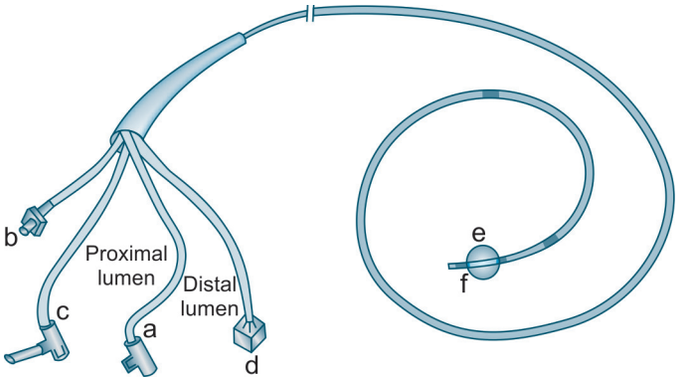

Fig. 5: Triple lumen pulmonary catheter. a = distal PA port, b = balloon inflation port, c = proximal RA port, d = thermistor hub, e = balloon, f = thermistor

60–110 cm in length, 4–7.5 Fr in caliber, with balloon inflation volumes ranging from 0.5–1.5 mL. The catheter material is polyvinyl chloride which is pliable at room temperature, and softens further at body temperature. The simplest type of catheter contains only two lumens, one to transmit PAPs, and the other for balloon inflation; however, the most commonly used one is the sophisticated triple-lumen thermodilution catheter. In fact, there are various types of catheters available and their use depends on the clinician's choice.

The *triple lumen 7.5 Fr thermodilution PA catheter* (Fig. 5) is 110 cm in length. The lumen of the distal PA port (a) runs through the length of the catheter to terminate at the tip, and is used to measure the PAP, and the pulmonary capillary wedge pressure (PCWP); mixed venous blood can also be drawn from this lumen. Drugs and hyperosmotic solutions should never be administered from the distal lumen as they may induce a local vascular or tissue reaction in a small pulmonary artery segment. The balloon inflation port (b) opens to a lumen that terminates within the balloon (e), which is situated just proximal to the catheter tip. The proximal RA port (c) opens to a lumen that terminates 30 cm from the tip of the catheter and lies in the right atrium (RA), when the tip of the catheter is in the PA. The RA port is used for monitoring RA pressure and also for administration of fluids. The RA port is also used to inject ice-cold saline during CO measurement, (d) represents the thermistor hub which is connected by wires to a small thermistor (f) located 3.5-4 cm proximal to the catheter tip. The thermistor records changes in the temperature over change in time during CO measurement; this is then relayed to an outside computer via the thermistor hub.

Further innovations to the three-lumen standard thermodilution PA catheter are also available. These include the *four-lumen thermodilution catheter* and its modified versions referred to as *position monitoring catheter,* which prevents distal migration of the catheter into the small branches of pulmonary arteries by signaling the need to withdraw the catheter.[22,23]

The newer *S-tip* catheters are designed for femoral vein insertion; similarly stiffer catheters (Swan-Ganz Hi-Shore from Baxter) are available, and may be used when more torque

control and maneuverability are needed, particularly during a femoral approach. Some new catheters available today are treated with antimicrobials and coated with heparin.

A *fibreoptic thermodilution PA catheter* is also available for continuous monitoring of mixed venous oxygen ($M\bar{v}O_2$); this has an additional channel that contains two fibreoptic bundles for light transmission. The light transmitted from outside is reflected back from the hemoglobin in the blood to a photodetector, which calculates the fraction of Hb saturated with oxygen, and displays it continuously on a bedside monitor.

Insertion Technique

Balloon catheters float easily from the vena cava to the pulmonary wedge pressure position, and knowledge of the various intracardiac waveforms is generally sufficient to be able to insert the catheter. Bedside fluoroscopy is not mandatory, and fluoroscopic equipment can be very cumbersome in an already small and cluttered ICU room. Besides, each patient's bed needs to be especially designed for imaging purposes, thereby adding to the overall cost. However, in cases with abnormal intracardiac flow patterns due to raised right ventricular pressures, the flow direction of the catheter may become very difficult and fluoroscopic guidance becomes necessary.

Percutaneously, a Seldinger technique is usually employed, which leaves an introducer catheter *in situ* through which the PA catheter is easily passed. These procedures have been described in detail in the Chapter Procedures in the Intensive Care Unit. There is no ideal site for PAC insertion, and this choice depends entirely on the operator's preference and expertise. In our unit, we prefer the subclavian or jugular site; femoral site is not commonly used except when subclavian or jugular sites are not accessible for various reasons. Many operators prefer to use the left subclavian vein as this approach offers the easiest route from the site of insertion to the RV due to its unidirectional bend.

Before insertion of the PAC, the pressure monitoring system should be set-up and kept ready as discussed earlier in this chapter. The catheter tip should be jiggled before insertion, and this produces sharp oscillations on the monitor. If no oscillations occur, there is probably an equipment malfunction, which should be corrected. The balloon should be tested by inflating with air as per the manufacturer's recommendations. After ascertaining the integrity of the balloon, the catheter is flushed with a sterile solution to ensure its patency and to remove all air.

Now with the balloon deflated, introduce the catheter through the introducer sheath into a central vein. Before advancing the catheter further, it is advisable to follow the markings on the catheter, as this gives a fair idea of the distance the catheter has traveled from the insertion point. In a normal adult to reach the RA, the catheter has to be advanced 10–15 cm from the subclavian vein, 15–20 cm from the right jugular vein, and 30–40 cm from the femoral vein. Under continuous pressure, monitoring with or without fluoroscopy, gently advance the catheter into the RA. Entry

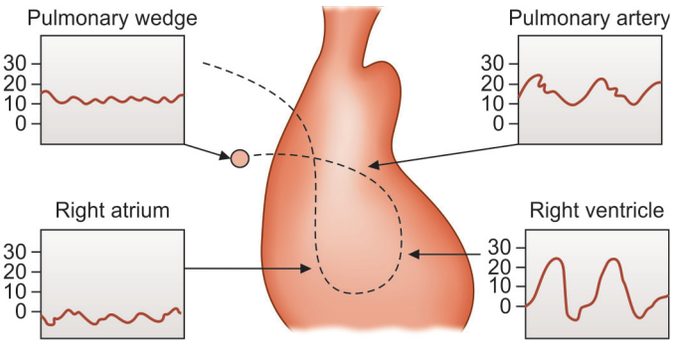

Fig. 6: Pressure waveform configuration as seen during the passage of the pulmonary artery catheter through the various chambers of the heart and in wedge position. The position of the catheter shown here is as seen on fluoroscopy

of the catheter tip into the thorax is signaled by increased respiratory fluctuations of the waveform. Once in the RA, inflate the balloon with air or CO_2 to the recommended volume (printed on the catheter). Never use fluids to inflate the balloon. In the presence of intracardiac shunts, CO_2 should be used instead of air for inflation of the balloon, in order to avoid systemic air embolization in case of accidental balloon rupture. Further, passage of the catheter from the RA to the pulmonary wedge position should normally not take longer than 30–40 seconds, provided there is no abnormal flow pattern in the heart or markedly elevated RV pressures. The shapes of the waveform and RV, PA and PCWP readings are used as a guide in advancing the catheter (Fig. 6). On entering the RV, the waveform is characterized by a steep upstroke, which is normally 3–4 times higher than the RA pressure. The sharp downstroke without a dicrotic notch dips to near zero, and then rises to reach a baseline plateau, which directly records the RVEDP, and is equal to the mean RA pressure. On advancing the catheter further into the pulmonary artery, another change in pressure waveform is noted, and this can be immediately differentiated from the RV waveform by the sudden elevation of the diastolic pressure and the appearance of the dicrotic notch. In the pulmonary vasculature, the inflated balloon acts as a sail, and continues with the flowing stream into the more peripheral branch of the pulmonary circulation where it will wedge. The catheter tip will now record a pulmonary wedge pressure tracing, which is very similar to the RA waveform (Fig. 6).

Correct Wedging Procedure

The balloon should not be allowed to remain inflated in the occluded position beyond 10–15 seconds. Inflation beyond this period can lead to pulmonary infarction. In addition, artifactually elevated pressures may result due to prolonged wedging. Upon deflating the balloon, the catheter recoils back toward the hilum into the main branch of the PA, and the PA waveform reappears. If the wedge tracings continue even after the balloon is deflated, the catheter should be carefully withdrawn to a point where PA waveforms reappear. The pulmonary wedge tracing should be obtained on reinflating

Table 4: Complications directly attributable to PAC

Complications	*Action/Prevention*
Arrhythmias	• Decrease insertion time • Use fluoroscopic guidance in high risk groups so that less maneuvering of catheter is necessary • Promptly remove catheter if arrhythmias persist
Infection	• Meticulous, sterile technique with all aseptic precautions during insertion and after care • Avoid repeated manipulations • Catheter to be removed at the earliest
Balloon rupture	• Inflation of balloon is typically associated with a feeling of resistance, the absence of resistance and failure to wedge suggest balloon rupture
Knotting	• Knots may be resolved by insertion of suitable guidewires and manipulation under fluoroscopy • If knot does not include any intracardiac structure, apply gentle traction to tighten the knot and then withdraw slowly • Only in worst cases, a thoracotomy and cardiotomy may be required
Clotting and thromboembolic complications in RA or systemic veins	• Intermittent flushing of catheters with heparinized saline • Avoid long standing catheter placements • Heparin coated catheters may reduce catheter thrombogenecity
Pulmonary infarction and PA rupture	• Avoid prolonged or over inflation of the balloon in the wedge position • Avoid repeated inflation of balloon for PCWP measurements; instead use PADP for continuous monitoring as PADP equals PCWP • Avoid inserting the catheter too far peripherally into a branch of PA. If catheter is seen beyond the hilum there is increased chance of infarction or rupture

the balloon to the recommended inflation volume; if the inflation volume is significantly lower than that recommended to produce a wedge trace, it implies that the catheter tip is still placed too far peripherally.

It is vital to remember that the mean pulmonary artery wedge pressure, which is normally equal to pulmonary artery diastolic pressure (PADP) may be lower in certain conditions associated with increased pulmonary vascular resistance (PVR). However, the PCWP is never higher than the PADP, and if so, it represents an artifact.

Lastly, the blood sample withdrawn from the catheter which is truly wedged, should represent and be equal to the oxygen saturation of arterial blood, whereas blood drawn from the pulmonary artery with the balloon deflated, gives the oxygen saturation of mixed venous blood, averaging 75%.

Normally, if there is a good correlation between PADP and PCWP, the PADP should be used to estimate the left atrial pressures instead of rewedging the catheter frequently. This reduces the risk of pulmonary vascular damage and pulmonary infarction, and also prolongs the balloon life.

Complications of Pulmonary Artery Catheterization[24]

All complications associated with a cutdown procedure or a percutaneous central venous catheterization can occur during PA catheterization. These complications have been discussed separately under the appropriate techniques in the Chapter Procedures in the Intensive Care Unit. Complications directly attributable to pulmonary artery catheterization and their prevention are discussed in Table 5.

Briefly, arrhythmias and possibility of infection are the most common complications. The occurrence of *arrhythmias*, and of ventricular ectopics in particular, are common during insertion of the catheter. The incidence is higher in patients with ischemic heart disease, ventricular failure, hypoxemia, digitalis toxicity, metabolic and electrolyte imbalance, and in patients with shock. Further, critically ill patients are commonly immunocompromised, and are frequently at a higher risk for *catheter-induced infections*.

Some less common causes are balloon rupture, knotting of the catheter, pulmonary thromboembolic complications and pulmonary artery rupture. Though *balloon rupture* by itself is not a dreaded complication, a remote possibility of embolization of balloon fragments to distal pulmonary circulation remains. Small caliber catheters are more likely to *knot* within the cardiac chambers and around other intravascular catheters. *Clots* occluding catheter lumen or the tip can result in inaccurate measurements; *thrombotic occlusion* can also occur in systemic veins or in the RA due to longstanding catheter placements. Persistent or repeated wedging of PAC or inadvertent migration of the catheter tip into smaller branches of pulmonary artery or prolonged balloon inflation can lead to *pulmonary infarction*. *PA rupture* though rare is the most dreaded of all complications with a high mortality rate. It may clinically result as mild hemoptysis to begin with but if ignored may progress to massive hemorrhage. In Table 4, details of problem solving and steps taken to prevent complications secondary to pulmonary artery catheterization have been discussed.

Pitfalls in Pulmonary Artery Pressure Measurement[25]

Several practical factors may be crucial in obtaining meaningful information whilst performing hemodynamic studies.

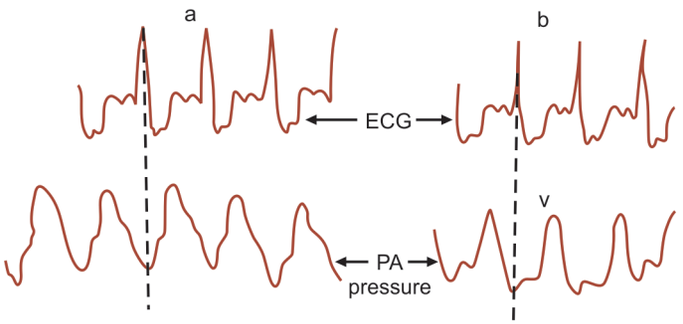

Fig. 7: Identification of v wave by superimposing the ECG on the pressure tracings. (a) PA tracing with the balloon deflated; the upstroke of the PA systolic wave starts near to the end of the QRS. (b) Balloon-inflated wedge tracing with superimposed v wave which is delayed by 200–300 msec after the QRS (see text)

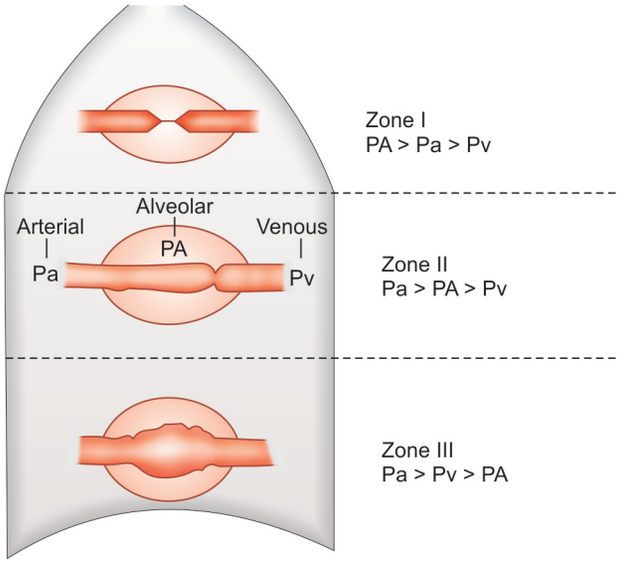

Fig. 8: Interrelationship between the alveolar and vascular pressures in the three West Zones. PA = alveolar pressure; Pa = pulmonary artery pressure; Pv = pulmonary venous pressure (see text for details)

Problems related to pressure lines, transducers and monitors, which commonly manifest as overdamped or underdamped waveforms, are common to both arterial and venous catheterizations. Similarly improper zero leveling and whip artifacts may be seen. All these problems have been discussed earlier in the Subsection on Pressure Monitoring System (Table 2). In addition to all these problems, PA waveforms in particular, are affected by cardiac dysfunction and by changes in intrathoracic pressures.

Cardiac dysfunction The PCWP waveforms consist of two distinct peaks: (1) the a and (2) the v waves. The more problematic, however, is the v wave which occurs in the presence of mitral insufficiency or significant mitral valve prolapse. This is a large v wave transmitted retrogradely from the LV, which is superimposed on the PCWP wave, thereby exaggerating its size; this may be wrongly interpreted as a pulmonary waveform even though the catheter is in the fully wedged position.

The v wave should be suspected if no PCWP waveform is seen despite the catheter being properly positioned in the wedge position. This can be confirmed by superimposing an ECG strip on both the balloon-inflated and balloon-deflated pressure tracings (Fig. 7). The v wave of the wedge waveform in the balloon-inflated tracing will be delayed by 200–300 msec after the QRS, whereas the upstroke of the PA systolic wave starts near the end of the QRS as shown in Figure 7.

Clinically, identification of v waves is important from two points of view. Firstly, once it is identified as a true PCWP waveform, and not a pulmonary artery waveform, the catheter need not be advanced any further into the peripheral pulmonary artery branch. Secondly, the correct pulmonary artery occlusion pressure should be read just prior to the upstroke of the v wave.

Artifacts due to ventilatory effects during spontaneous breathing During normal quiet breathing, inspiration or chest expansion requires a slightly negative intrapleural pressure (subatmospheric), whilst expiration requires a slightly positive intrapleural pressure (near atmospheric). These cyclic changes in the intrathoracic pressure are transmitted to the intravascular pressure tracings, creating a minimally wandering baseline, with expiration producing positive deflections, and inspiration producing negative deflections. These pressure changes are insignificant, and minimally affect the mean PCWP. However, in case of marked labored breathing, as in patients with acute lung injury or COPD, greater swings in pleural pressures are required to move air in and out of the lungs. As a result there is a wide fluctuation in the pressure waveform baseline. This leads to inconsistent and inaccurate recordings. In such a situation, it is best to disregard the digital display and record a long tracing of the PAP or PCWP waveforms, and read that portion of the waveform that corresponds with end-expiration. It should however be noted that in patients on mechanical ventilation, the end-expiration is reflected by the negative deflection of the wandering pressure baseline.

Artifacts due to influence of gravity[25] Pulmonary artery pressures increase progressively down the lung, as the blood flow increases in the lower parts of the lung due to the influence of gravity. However, the alveolar pressures remain equal throughout. West divided the lung model conceptually into three zones, called the West Zones (Fig. 8), which illustrated the interrelationship between the alveolar and vascular pressures and the effect of gravity.

Zone 1 is the uppermost portion of the lung or apex in an upright person. This is an area with potentially low vascular pressure, hence, alveolar pressures here exceed both the PAP and the pulmonary venous pressure (PVP) (Alveolar pressure > PAP > PVP). If a wedged catheter tip is placed in this position, it will not reflect the LA pressure as the continuous conduit between the catheter tip and the LA is occluded by the higher alveolar pressure, but will reflect only the alveolar pressure.

Zone 2 is represented by the middle portion of the lung and here too the alveolar pressure is greater than PVP, but

less than PAP. However, during end-expiration and inspiration the alveolar pressure is at its lowest, and does not occlude the pulmonary veins, thus allowing the wedged catheter tip to accurately reflect the LA pressure; however, during end-inspiration and early expiration, the elevated alveolar pressure will pinch the pulmonary veins, and the wedged catheter once again shows an erroneously high PCWP.

Zone 3 is at the bottom of the lung, where there is increased blood flow due to gravity, and vascular pressures are greatest. Hence, both the PAP and the PVP far exceed the pulmonary alveolar pressure, producing a constant open vascular conduit from the catheter tip to the LA, which allows the PCWP to accurately reflect the LA pressure in all phases of respiration.

To confirm the Zone 3 catheter position one should constantly be able to identify the wedge waveform. A damp tracing in absence of other problems suggests a Zone 1 or Zone 2 position. A lateral chest X-ray can also ascertain the proper catheter position; a Zone 3 position can be confirmed if the catheter tip is seen to lie at, or below the left atrial level. Lastly, in patients on positive end-expiratory pressure (PEEP), the PCWP should not be influenced by sudden increase or decrease in PEEP levels if the catheter is properly positioned in Zone 3.[26]

The three zones described above hold true for an individual in an erect position, and as measurements are so often made with the patient upright or semi-inclined, it is important to place the catheter tip at or below the left atrial level, confirming the Zone 3 condition. However, in the supine position, most of the alveolar capillary units fall in the gravity-dependent area of the lung having the characteristics of Zone 3 condition, and as most of the blood flows in this area, the PA catheter invariably floats into Zone 3.

Artifacts due to effects of mechanical ventilation and PEEP

Positive changes in the airway pressures produced by mechanical ventilation reflect on the heart and vascular structures of the thorax. This can lead to inaccurate measurements and wrong interpretation of hemodynamic parameters for three reasons.

1. Measured PAP and PCWP will increase during the delivery of each mechanical breath. However, the pressure at end-expiration should be the same as with spontaneous breathing, and therefore it is important that the measurements are recorded at end-expiration.
2. Mechanical ventilation has the potential to decrease CO by increasing the intrathoracic pressure and thus reducing the venous return to the heart. In addition, the positive pressure surrounding the heart may produce a tamponade effect, further interfering with the diastolic filling. Though the CO may fall, the CVP, PAP and PCWP may rise because of perivascular compression distorting the volume-pressure relationship. In other words, pressures that appear to be normal may be insufficient to ensure adequate preload and CO.
3. Positive alveolar pressure may increase the Zone 1 and 2 conditions, so that a considerable anatomical area of Zone 3 now takes on the characteristics of Zones 1 and 2, especially if the PAP is low. This will lead to inaccurate measurements as PCWP will no longer reflect the LA pressure correctly, even though the catheter tip seems to lie in Zone 3 on X-ray.

All these above-mentioned effects of mechanical ventilation will be exaggerated in patients on either PEEP, or continuous positive airway pressure (CPAP). Generally, PEEP levels less than 10 cm of H_2O do not compromise the measurements of PCWP or CO very significantly. However, PEEP levels greater than 10–15 cm H_2O certainly increase the disparity between the PCWP and LA pressure relationship, and also compromise cardiovascular function.

In order to obtain more accurate LA pressure measurements by measuring PCWP in patients on high levels of PEEP, one has to assume that approximately 50% of the PEEP is transmitted to the LA. As PEEP is measured in centimeter of water, and PCWP in mm Hg, a simple calculation would be to subtract 1.5 mm Hg pressure from PCWP for every 5 cm of H_2O of PEEP administered (as 1 mm Hg = 1.36 cm H_2O). For example, if a PCWP of 28 mm Hg is recorded in a patient on PEEP of 20 cm H_2O, the patient's corrected LA pressure should read 6 mm Hg less, i.e. 22 mm Hg.

Many clinicians prefer to disconnect the patient from the mechanical ventilator during PCWP measurements; this practice should however be discouraged. As long as the pressure tracings show the characteristic PCWP waveforms, and one-half of PEEP is approximately subtracted from the PCWP, it seems reasonable to measure the pressures that apply to the patient during therapy, rather than during a brief interval without it. On the other hand, on discontinuing mechanical ventilation or PEEP, a sudden change in hemodynamics occurs because of an increase in venous return, and the measured parameters may be different from those that exist when the patient is on ventilator support.

CARDIAC OUTPUT MEASUREMENT BY THE THERMODILUTION TECHNIQUE[27,28]

The Fick oxygen consumption method described by Adolph Fick in 1870 is usually considered to be the gold standard to which other methods are compared because of its extreme accuracy in measuring the CO. However, this method is not practical for day-to-day use in the ICU as it is time consuming, and requires the patient to be in a steady metabolic state.

The indicator dye dilution technique is another method of measuring CO, but this too is not a practical bedside procedure.

The thermodilution technique is currently the most widely used method in clinical practice. Though first introduced by Fegler in 1954, its first reported use in humans was published by Margaret Branthwaite and Ronald Bradley in 1968.[29] The basic principle underlying this method is the detection of the change in temperature of blood over a period of time; this can be accomplished by injecting cold saline in the RA from a proximal port of the PA catheter, whilst the thermistor on the catheter tip detects the temperature change in the PA. This change is inversely proportional to the blood flow.

Procedure

The main equipment required for CO monitoring is the CO computer and a thermodilution PAC. Also needed are five to six 10 mL sterile plastic syringes, an injectate solution (usually ice cold normal saline), an injectate temperature probe and catheter connecting cables. It goes without saying that aseptic precautions should be observed throughout the procedure. The patient should be preferably supine, but a semi-reclined position (<20°) should not alter the CO. A more erect position, particularly in critically ill patients on potent vasodilators, can produce orthostatic hypotension; hence in such patients relative changes in position during serial measurements can affect the reliability of the CO readings.

Prior to injection, the position of the thermodilution catheter should be ascertained. The catheter tip must lie in the pulmonary artery and should not be in the wedged position. The balloon must be deflated prior to injection and the thermistor hub should be connected to the CO monitor via the catheter connecting cable. The injectate probe should be connected to the CO computer, with the sterile probe dipped into the injectate solution.

About 10 mL of 0.9% saline or 5% dextrose (ice cold solution or solution at room temperature, depending on the method used), is injected within 4 seconds as a bolus through the proximal port of the PA catheter. Lesser volumes, or prolonged injection times can give unreliable measurements. The cold solution mixes with the blood in the right heart chamber lowering the blood temperature, the cooled blood flows into the PA, and the thermistor at the catheter tip records the temperature change and relays this information to the CO monitor. The CO computer calculates the temperature difference between the injectate solution and the blood, and displays the temperature-time curve. The area under the curve is inversely proportional to the flow rate in the PA, which is representative of the CO.

The injectate used need not be an ice cold solution, as solutions at room temperature also produce reliable results. It is also important that serial measurements should be obtained, after discarding the first trial which is often unreliable. The average value of three measurements is taken as the CO, provided that they do not differ from each other by more than 15%. The injections should be always timed during end-expiration to avoid unacceptable variations in CO, which may occur during different phases of the respiratory cycle. This is particularly important for patients on mechanical ventilator support. However, it may be impossible to start and complete injection precisely during one phase of the respiratory cycle. To overcome this practical difficulty, it is reasonable to time the starting of the injection at the onset of inspiration; it may take 2–4 seconds to reach the thermistor, and this should produce the thermodilution curve close to the end of expiration.

Pitfalls in CO Monitoring

Erroneous CO readings may be produced by conditions such as tricuspid regurgitation, or by a clot partially blocking the catheter lumen, or due to intracardiac shunts. In case of right to left shunts, the CO is falsely high because part of the cold injectate crosses the shunt and the temperature difference sensed by the thermistor in the PA is less; in left to right shunts, falsely elevated readings are obtained as the blood volume in the right side of the heart is increased, and the injectate is diluted, once again decreasing the temperature difference in the PA, and producing a curve with a reduced height.

Besides other technical points, the temperature and volume of the injectate solution must be precisely determined to avoid errors in CO measurements. A larger volume will produce a greater temperature change in the pulmonary circulation, which is interpreted by the monitor as a low CO. Conversely, a lesser volume will produce a smaller temperature change, which will be interpreted as a high CO.

If the injectate solution is at room temperature, producing very minor temperature changes, the serial CO readings will be less reproducible. This is therefore the practical disadvantage of using a room temperature injectate instead of an ice cold solution. Similarly, the reproducibility of the measurements may be affected despite using iced injectate, if there is a significant temperature change between the time the solution is drawn and the time it is injected. However, several systems are available today that measure the injectate temperature at the time it enters the proximal port of the PAC. This minimizes injectate temperature errors, and improves the reproducibility of the measurements.

Continuous CO Monitoring

Continuous CO measurements using thermodilution techniques are also available. Instead of cold water, a small heating filament at the end of the catheter warms pulmonary blood and a downstream sensor records changes in temperature. These measurements are found to lag behind by a few minutes, but they are reliable and able to provide near real-time COs. Most minimally invasive and noninvasive methods including continuous monitoring of mixed venous oxygen saturation ($S\bar{v}O_2$) or its surrogate central venous oxygen saturation ($Sc\dot{V}O_2$) described next also enable continuous CO monitoring.

MIXED VENOUS O_2 SATURATION ($S\bar{v}O_2$) AND CENTRAL VENOUS O_2 SATURATION ($Sc\dot{V}O_2$)[30]

Saturation of mixed venous oxygen ($S\bar{v}O_2$) is the saturation of mixed venous blood drawn from the pulmonary artery through a PAC. It is usually though not always, a good indicator of the adequacy of tissue oxygenation and it reflects the balance between oxygen demand and supply to the tissues (Table 5).

The oxygen saturation of blood in the pulmonary artery, which represents the $S\bar{v}O_2$ can be monitored continuously by using special fiberoptic thermodilution catheters, or intermittently by obtaining serial samples of blood drawn from the distal lumen of the PAC. The technology for measuring $S\bar{v}O_2$ is based on reflection spectrometry. This involves

Table 5: Conditions affecting $S\bar{v}O_2$

Decrease in $S\bar{v}O_2$	*Increase in $S\bar{v}O_2$*
Poor O_2 supply— • Decreased CO • Anemia • Hypoxic hypoxia	Impaired O_2 utilization— • Sepsis • Cyanide poisoning
Excessive O_2 demand— • Fever • Seizures • Increased metabolic rate • Increased physical activity	Decrease in O_2 demand— • Hypothermia • Prolonged anesthesia

sending light of selected wavelengths down one fiberoptic filament in the catheter body to blood flowing past the catheter tip. The reflected light is then transmitted back through the second fiberoptic filament to a photodetector located in the optical module. Hemoglobin and Oxyhemoglobin absorb light at different wavelengths, and the reflected light is analyzed to obtain the $S\bar{v}O_2$.

In a normal individual, $S\bar{v}O_2$ ranges from 60% to 80%. It is generally accepted that $S\bar{v}O_2$ should be considered clinically significant if the value is outside the normal range or if a change in $S\bar{v}O_2$ of 5–10% from the baseline value persists for greater than 3–5 minutes, even if the value is in the normal range. A marked fall in $S\bar{v}O_2$ generally indicates inadequate tissue oxygenation, and the fall is attributed to a decrease in SaO_2, Hb concentration, or the CO or to a marked increase in $\dot{V}O_2$. When thermodilution techniques are not available, serial measurements of $S\bar{v}O_2$ are frequently used to monitor changes in the CO, provided that the Hb concentration remains constant, and the PaO_2 does not fluctuate significantly.

In non-shock conditions, there is a good correlation between $S\bar{v}O_2$ and oxygen saturation obtained from a central vein ($Sc\dot{V}O_2$) but not so in case of circulatory shock. However, changes in both parameters run parallel so that changes in $S\bar{v}O_2$ indicating a hemodynamic derangement are mirrored by appropriate changes in $Sc\dot{V}O_2$. Similarly, changes in $S\bar{v}O_2$ due to therapeutic interventions are well reflected by changes in $Sc\dot{V}O_2$ even in patients with severe shock. Hence, in day to day clinical practice it is simpler and less invasive to measure $Sc\dot{V}O_2$ from a CVP line as a surrogate of $S\bar{v}O_2$.[31]

MINIMALLY INVASIVE CARDIAC OUTPUT MONITORING[32,33]

It should be emphasized that introducing new technologies for non/minimally invasive monitoring systems will not necessarily influence outcomes; unless it is demonstrated, that the measured parameters are absolutely reliable and can be translated easily into therapeutic interventions, with a high degree of confidence. This is why we still believe that PAC in a selective group of patients is a valuable monitoring tool especially when used by adequately trained physicians to correctly interpret and apply the data provided.[34] Currently available minimally invasive CO measuring devices are based on the following principles (Table 1)—

- ❑ Pulse pressure analysis.
- ❑ Doppler.
- ❑ Applied Fick principle of dye dilution.
- ❑ Bioimpedance.
- ❑ Plethysmographic indices.

Pulse Pressure Analysis

By this method, SV can be estimated continuously by analyzing arterial pulse waveform, which is derived from an indwelling arterial line. Briefly, this method involves the calculation of the area under the systolic portion of the arterial pressure waveform, which when divided by the aortic impedance allows estimation of the LVSV. Basically, these devices are of two kinds: (1) those requiring calibration and (2) those which are self-calibrated.

Systems requiring calibration The pulse induced contour cardiac output (PiCCO)[35] is based on the above principle but requires calibration by transpulmonary thermodilution to obtain accurate CO measurements. It therefore requires a central venous line placement with a temperature sensor on the distal lumen and a thermodilution sensor at the arterial catheter end. Calibration is required to measure the aortic impedance and needs to be repeated at least every 8 hours in a hemodynamically stable patient and at shorter intervals under certain conditions. This is necessary in order to calculate the SV from a pressure trace because the algorithm used by these devices has to compensate for the overall impedance of the system, based on both the compliance and resistance of the cardiac vasculature.

Once calibrated, the system computes LVSV by measuring the area under the systolic part of the arterial waveform from end diastole to the end of the ejection phase and then dividing this area by the aortic impedance; the SV is thereby continuously monitored.

Further, information, such as intrathoracic blood volume (ITBV), extravascular lung water (EVLW) and stroke volume variation (SVV), is derived by application of appropriate inbuilt formulae. ITBV is a volumetric measure of cardiac preload (LVEDV) and changes in ITBV correlate with changes in CO and can be used as a surrogate for a patient's fluid status. EVLW on the other hand serves as an early warning during fluid resuscitation by estimating the water content extravasated in the lung tissue as in ARDS or cardiac failure. Studies have shown that resolution of pulmonary edema may be more rapid when EVLW is used as a guideline and prognostically there was higher risk of mortality when EVLW was greater than 14 mL/kg.[36]

Similar to the PiCCO system is the newly introduced EV 1,000 per volume view system, which also requires calibration and though the manufacturer's claim it to be comparable to PiCCO in tracking CO, it needs further studies for clinical validation. For both these systems, the company manual should be referred for procedural and calibration details.

Alternatively a new technique is the LiDCO plus system[37] which is also a PPA device requiring a central venous access

and calibration for vascular compliance. However, it uses a pulse power analysis in contrast to PiCCO, which uses a pulse contour device, but this is only a modification in a technical sense to circumvent certain theoretical problems of the pulse contour analysis. LiDCO is an abbreviation for lithium dilution CO. Here, calibration is done by using lithium chloride injected via a central line and collecting the blood that flows past a lithium sensor attached to the patient's existing arterial line, thereby it is not affected by thermal influences. The main limitation of this device is that if a muscle relaxant has been used on the patient, it can cross react with the lithium sensor resulting in unreliable readings. Hence, the calibration should be done prior to the use of muscle relaxants.

Self-calibrated devices Methods, like PiCCO described earlier, require regular manual calibration from time to time as they cannot automatically correct the patient's changing vascular tone. Therefore, the accuracy of these techniques is highly dependent on the delay between two normal calibrations and on the hemodynamic stability of the patient. A self-calibrated method (Flo Trac/Vigileo,[38] Edwards Lifesciences) has been in use since 2005, and the latest 3rd generation version is able to update the self-calibrated CO every 20 seconds. This is an improvement over the earlier generation softwares.

Briefly, in this method the CO is computed from the following equation—

$$CO = \text{Pulse rate} \times APsd \times K$$

where, APsd is the standard deviation of the arterial pressure and K is an autocalibration factor derived from a proprietary multivariate equation, which includes biometric variables (e.g. age and sex) that are known to affect the arterial compliance. This 3rd generation software is based on a large human database containing memory recordings from septic and liver transplant patients who are often vasodilated. This makes the 3rd generation software far more accurate (even in presence of a low SVR) than the earlier softwares based on a limited database.

The monitoring device consists of a transducer (Flo Trac) that is connected to a standard radial or femoral arterial catheter and to a Vigileo monitor. It is important to keep the Flo Trac sensor level to the phlebostatic axis at all times to ensure accuracy of CO. The step-by-step methodology for Flo Trac sensor set up, Vigileo monitor set up and zeroing techniques are well described in the Edwards Quick guide to cardiopulmonary care available from Edwards Lifesciences.

Other self-calibrated devices available in the market are shown in Table 1.

NONINVASIVE MONITORING DEVICES

Noninvasive Pulse Pressure Analysis[39]

These devices monitor continuous CO noninvasively without an arterial line, using instead a finger cuff to reconstruct a brachial artery pressure waveform. One of the available monitors (Nexfin) calculates the CO on a beat to beat basis by dividing the integrated pulse systolic area by the aortic impedance which in turn is derived from a predetermined model incorporating patient specific aortic mechanical properties. So far only limited clinical validation studies are available; however, it has shown acceptable CO values when compared with thermodilution performed by PAC. Such noninvasive monitors have a great potential in critical care setting where tracking the CO for early hemodynamic intervention is required and where invasive modalities are not readily available.

Transesophageal Doppler Monitoring Devices[40]

Doppler ultrasound can provide a relatively noninvasive and continuous real time quantification of CO. It involves inserting a flexible probe into the mid-thoracic esophagus where it lies in close proximity to the aorta without any signal interference from other anatomical structures. A pulse wave Doppler transducer placed in the probe tip calculates the changes in blood flow velocity in the descending aorta. Aortic diameter is estimated by using a normogram after entering age, gender, height and weight of the patient. The aortic diameter can also be assessed by M mode echocardiography, which allows for the actual measurement of the aortic diameter, eliminating the possible error associated with normogram based estimates. Once the cross-sectional area of the aorta is known, SV can be derived from the blood flow velocity (i.e. multiplying cross-sectional area of the aorta by blood flow velocity). As the measurements are made in the descending aorta it represents only 70% of the total CO since coronary and brachiocephalic flows are not measured, creating a partition between caudal and cephalic blood supply areas. Clinical validation studies initially had shown conflicting results; however, a recent meta-analysis reviewing all validation studies confirms reliability of CO measurement in clinical practice.

Transesophageal Echocardiography (TOE)[41]

In this method, one uses a combined 2D Echo and Doppler approach to measure the CO. The 2D Echo measures the diameter of the aortic annulus in mid-systole, which allows the calculation of the flow cross-sectional area; this when multiplied by the velocity of blood flow across the aortic valve measured by the aid of Doppler gives the CO. It is necessary to ensure that blood flow is parallel to the path of the pulse wave Doppler ultrasound. In experienced hands, TOE can give valuable hemodynamic information and in addition can identify presence of vegetations in infective endocarditis or the presence of pericardial effusion. The 2D Echo measurement of aortic valve diameter is clinically well established and of proven accuracy; however, it is challenging time-consuming and requires training and skill. For instance, a wrongly measured diameter can be magnified when squared (as required in the equation), or if the angle between the Doppler beam and blood flow is not exact, it will lead to an underestimation of velocity.

Table 6: Normal hemodynamic values

Variables	*Abbreviations*	*Units*	*Normal range*
Right atrial pressure	RAP	mm Hg	0–6
Mean pulmonary artery pressure	MPAP	mm Hg	11–15
Pulmonary capillary wedge pressure	PCWP	mm Hg	3–15
Cardiac index	CI	L/min-m^2	2.8–3.6
Left ventricular stroke work index	LVSWI	g-m/m^2	44–68
Right ventricular stroke work index	RVSWI	g-m/m^2	4–8
Systemic vascular resistance index	SVRI	dynes-sec/cm^5-m^2	1700–2600
Pulmonary vascular resistance index	PVRI	dynes-sec/cm^5-m^2	100–225
Oxygen delivery index	DO_2I	mL/min-m^2	500–650
Oxygen consumption index	VO_2I	mL/min-m^2	110–150

There are many other minimally invasive monitoring devices available in the market which are still not very widely used in clinical practice. *Applied Fick Principle*[42] based on partial CO_2 rebreathing method (NICO System) is one such method. *Bioimpedance* and *Bioreactance (NICOM)* are some of the other available methods. Thoracic electrical bioimpedance is a technique, which is based on correlating changes in aortic flow throughout the cardiac cycle with changes in electrical impedance of the thoracic cavity. In contrast, bioreactance mode of monitoring CO involves delivery of an oscillating current and the variation in the frequency spectra that occurs when the current traverses the thoracic cavity; it relies only on the analysis of the changes occurring in the signal amplitude. Validation studies for all these three techniques though showing occasional discordances were in most instances comparable with thermodilution and other techniques.[33,43]

HEMODYNAMIC VARIABLES AND THEIR CLINICAL APPLICATION[44-46]

Determinants of Ventricular Performance

Pulmonary artery monitoring allows us to obtain various hemodynamic variables, which are either directly measured or derived by using specific calculations (Table 6). These help us to understand the determinants of cardiac performance, and factors influencing oxygen transport, thereby providing a better perception of cardiovascular hemodynamics at the bedside.

The *stroke volume* (SVI) is the volume of blood ejected by the heart during each contraction, and is a very important indicator of ventricular performance. It is calculated by dividing the CO by the heart rate, and when indexed to the body surface area (BSA), the normal stroke volume index (SI) is arrived at (normal range is 35–45 mL/m^2). The three most important physiological determinants of SV are: (1) preload, (2) afterload and (3) myocardial contractility.

Preload refers to the length of the cardiac muscle fibers at the start of ventricular contraction; this is equal to the left ventricular end-diastolic volume (LVEDV), and is clinically measured as LVEDP. The PCWP, which is directly measured by a well-positioned PAC, in the absence of left ventricular inflow obstruction, gives an indication of the relative changes in the preload. However, this is true only if the ventricular compliance is static; in a diseased heart the LVEDP and the LVEDV may not correlate, as the ventricular compliance is altered. For instance, in dilated cardiomyopathy, the ventricular compliance increases, and a large increase in the ventricular filling volume is accompanied by only a small change in the filling pressure. On the other hand, in a stiff non-compliant ventricle seen in ischemic heart disease, the ventricular filling pressure increases disproportionately to the ventricular filling volume. Hence, the clinical importance of maintaining a slightly higher LVEDP in cases of acute myocardial infarction, in order to achieve an adequate CO, cannot be overstressed.

Afterload is defined as the impedance to blood flow from the ventricle. Whilst preload determines the force of the ventricular contraction, afterload denotes the tension developed by the cardiac muscle during systole as a result of systemic vascular resistance (SVR). Resistance is typically calculated as a pressure gradient divided by mean flow. Hence, the resistances to the two ventricles (indexed to the BSA) are derived by the following equations—

$$\text{SVRI} = \frac{\text{Mean arterial blood pressure} - \text{CVP}}{\text{Cardiac Index}} \times 80$$

$$\text{PVRI} = \frac{\text{Mean pulmonary artery pressure} - \text{PCWP}}{\text{Cardiac Index}} \times 80$$

The normal range of values is given in Table 7.

The SVRI is usually raised in cardiogenic and hypovolemic shock, in systemic hypertension and with the use of vasoconstrictor drugs. It is characteristically low in septic shock, thyrotoxicosis, anemia, cirrhosis and with vasodilator therapy. The PVRI is primarily raised in pulmonary edema, following pulmonary embolism, and in some valvular or congenital heart diseases. It is also raised in hypoxemia, due to pulmonary vasoconstriction.

Table 7: Hemodynamic changes caused by some commonly used IV drugs

Drugs	*HR*	*MAP*	*PCWP*	*CO*	*SVR*
Nitroprusside	↑	↓	NC or ↓	↑	↓
Nitroglycerin	↑	↓	↓	↑	↓
Norepinephrine	NC or ↑	↑	↑↓	↑, NC	
Dopamine	NC or ↑	NC or ↑	NC or ↑	↑	↑
Dobutamine	NC or ↑	NC or ↑	NC	↑	NC
Amrinone	NC	↓	↓	↑	↓

Key: NC = No change; * Dose related; ↑ = increased; ↓ = decreased.

Contractility is the inotropic state of the cardiac muscle, and may be expressed as the velocity of muscle fiber shortening during systole. It is important to realize that contractility is independent of preload or afterload, and at present we have no bedside method of monitoring cardiac contractility. However, if two of the three fundamental factors determining SV (viz. preload and afterload) can be kept constant, then obviously the changes in stroke work performed by the ventricle become the determinant of ventricular function, and give a good idea of the inotropic state of the heart. The stroke work for the two ventricles (indexed to the BSA) is calculated as follows—

$$\text{LVSWI} = \text{SI} \times (\text{MAP} - \text{PCWP}) \times 0.0136 \text{ g.m/m}^2$$
$$\text{RVSWI} = \text{SI} \times (\text{MPAP} - \text{CVP}) \times 0.0136 \text{ g.m/m}^2$$

The normal range of values is given in Table 7.

The basic relationship between preload, afterload and contractility is best described by Starling's pressure curves, which are plotted by obtaining responses of LV filling pressure (PCWP) and SV to fluid challenge. LV performance can be judged by plotting such a curve; however, one cannot be sure if a good or poor response is due to increased or decreased contractility, or is secondary to an alteration in the afterload.

Hemodynamic parameters can be greatly influenced by drug therapy, which may rapidly change the hemodynamic status of a critically ill patient. Hence, it is important to know the pharmacological influence of the drugs commonly used in the ICU, on the hemodynamic variables (Table 7).

DETERMINANTS OF OVERALL CIRCULATORY FUNCTION AND TISSUE PERFUSION

The importance of arterial oxygen content, the oxygen delivered to the tissues, oxygen consumption by tissues has been dealt with in the Chapter Basic Cardiorespiratory Physiology in the Intensive Care Unit to which the reader is referred. These are important parameters that help the intensivist to assess the overall hemodynamic state.

ASSESSMENT OF TISSUE PERFUSION[47]

Variables that may assist tissue perfusion are shown in Table 8. Tissue hypoperfusion can be present even in patients with a normal blood pressure and an adequate CO and is commonly referred to as cryptic shock or microcirculatory failure. Microcirculatory failure has been discussed in the Section Clinical Shock Syndromes.

Table 8: Variables that may assist with tissue perfusion

Global	*Organ or Regional*
Hypotension, tachycardia mottled skin, delayed capillary refill, altered mental status	Raised serum bilirubin and/or liver transaminases Elevated cardiac enzymes
Hyperlactemia	Side-stream dark-field video microscopy
Low cardiac output (but not necessarily so)	Gastric tonometry
Low mixed venous oxygen saturation	Sublingual capnometry
Low central venous oxygen saturation	Near infra-red spectroscopy

At the bedside tissue perfusion should be judged clinically—cold peripheries, sweating, poor capillary refill, mental obtundation, fall in urine output. There may be tachycardia, bradycardia or the heart rate may be normal. Hypotension is usually present but not necessarily so. Overall poor tissue perfusion is associated with a rise in blood lactate levels.[48,49] A progressive rise in lactate levels is associated with worsening prognosis.[50] Also a rapid fall in the lactate level following resuscitation denotes a better prognosis.[51,52]

These are features that characterize global tissue hypoperfusion. A lot of research is today being conducted on methods to determine regional tissue perfusion. *None of these methods which are referred to below have been shown to provide information that ultimately benefits patient outcome.*

Methods to determine regional tissue perfusion are gastric tonometery,[53-56] which by measuring the local PCO_2 within the stomach lumen assesses the perfusion status of the gastric mucosa; side-stream dark field videomicroscopy; sublingual capnometry and near infrared spectroscopy (see Section Clinical Shock Syndromes).

MEASUREMENT OF STROKE VOLUME VARIATION AND ARTERIAL PULSE PRESSURE VARIATION

Stroke volume variation (SVV) and arterial pulse pressure variation (PPV) are dynamic measurements that help to better assess the likely responsiveness of the ventricles to a fluid challenge as compared to the measurements of the CVP and the PCWP. Here, fluid responsiveness correlates with the preload responsiveness part of the Frank Starling Curve (Fig. 9).

Stroke Volume Measurement (SVV)

Studies have shown that SVV in patients on MV is highly predictive of preload responsiveness. However, dynamic

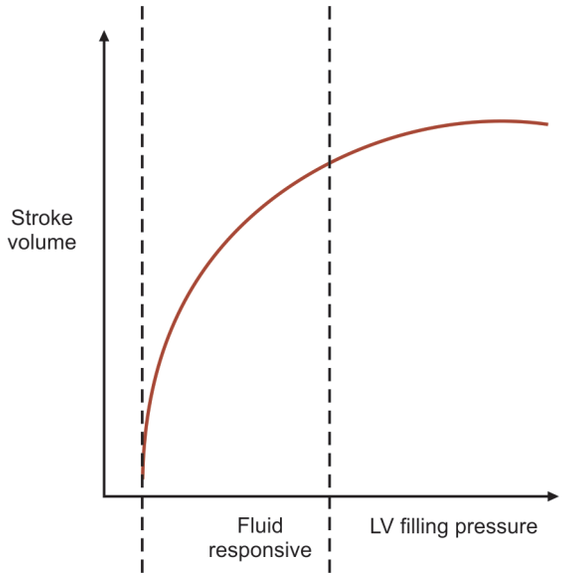

Fig. 9: Cardiac performance

indicators lose their validity during spontaneous non-uniform breathing. Hence, monitoring of SVV requires the patient to be on MV and properly sedated to attain uniform ventilation. Similarly, these parameters will lose their predictive value in presence of irregular R-R intervals as in atrial fibrillation. SVV greater than or equal to 10% predicts an increase in CO of greater than or equal to 15% for a bolus of 500 mL of fluid. SVV can be assessed directly by the esophageal Doppler or by pulse pressure analysis using devices, such as PiCCO, LiDCO or FloTrac systems, described earlier in this chapter.

Arterial Pulse Pressure Variation

Pulse pressure variation is a fairly reliable alternative being more practical and showing reasonable accuracy. Arterial pulse pressure defined as the difference between systolic and diastolic pressures is directly proportional to LV stroke volume and inversely related to arterial compliance. Hence, the respiratory variations in the pulse pressures reflect the changes in LV stroke volume and become a marker for preload dependence. PPV is calculated as a percentage, i.e. PPV % = (Ppmax – Ppmin)/[(Ppmax – Ppmim)/2] × 100 where Ppmax is the difference between maximum systolic and maximum diastolic pressures and Ppmin is the difference between the minimum systolic and minimum diastolic pressures. A PPV of greater than 13% implies 85% probability that the patient will benefit by fluid administration. Once again here, the parameters will lose their predictive value and accuracy under conditions of varying RR intervals (atrial fibrillation) or varying tidal volume; hence the patient has to be sedated and on MV during the measurements.

Entirely noninvasive methods that predict the response of the ventricles to fluid-loading are the measurement of the inferior vena cava (IVC) diameter during respiratory variation by an M mode echocardiography and estimation of the Massimo Continuous noninvasive Pleth Variability Index (PVI).[57,58] Both these methods are only applicable to patients who are sedated and on ventilator support.

Many of these methods used for dynamic measurements may not be available readily in most ICUs in our country. It is doubtful if these methods have shown as yet any improvement in outcome in patients with shock. *The clinical response of the patient to a volume challenge, even today, is the sheet anchor to gauge the presence or absence of ventricular responsiveness to an increase in preload.*

SUMMARY OF HEMODYNAMIC MONITORING

1. The main indication of hemodynamic monitoring, and more specifically of PA catheterization, will always depend on the risk-benefit ratio as judged by the clinician. However, it is invaluable in monitoring fluid administration, inotropes, vasopressor and vasodilator therapy in critically ill patients with shock, acute lung injury or multiple organ dysfunction.
2. The accuracy and reliability of all invasive hemodynamic measurements depend mainly on the correct method of assembling and calibrating the pressure monitoring equipment.
3. In most centers in India, CVP monitoring is common, and may be considered to be quite reliable, provided its limitations (as discussed earlier) are fully appreciated.
4. The following criteria should be fulfilled if PA pressure monitoring is to be used as a measure of left ventricular preload: (a) a normal ventricular compliance, where the LV pressure-volume relationship can be predicted; (b) absence of LV inflow obstruction; (c) unobstructed vasculature in the pulmonary capillary bed.
5. It is not advisable to disconnect the mechanical ventilator or remove PEEP during PCWP measurements. On the contrary, the measurement of pressures during therapy (with appropriate correction for PEEP) is more relevant and meaningful.
6. Catheter-induced sepsis is the commonest of the long-term complications of pulmonary artery catheterization in our part of the world, and hence, strict asepsis should be observed. Pulmonary artery rupture, though rare, is the most dreaded complication, and carries the highest mortality.
7. It is important to understand and differentiate the various determinants of cardiac and circulatory functions and measurements of tissue perfusion. It would be inappropriate to treat perfusion failure entirely with the concepts and therapy designed for cardiac failure. Hence, for overall management, it is important to understand the failure of each circulatory component.
8. The goal of noninvasive monitoring is not just attaining comparable information vis-à-vis invasive monitoring,

but the information attained should be continuous and in real time. Another important advantage of noninvasive monitoring would be to provide information early, possibly in pre-ICU locations such as in the casualty room. Once the hardware and software innovations of these monitoring devices attain acceptable accuracy, reliability and cost-effectiveness, it may change the standards of management of acutely ill patients with early hemodynamic impairment.

9. Tissue hypoperfusion, when present in patients with normal blood pressure and CO, is commonly referred as microcirculatory failure.
10. Measurement of SVV and arterial PPV are comparatively new technologies that help to assess the likely increase in ventricular responsiveness to volume load.

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CHAPTER 8

Respiratory Monitoring in Adults

GENERAL CONSIDERATIONS

Respiratory monitoring is merely one facet in the overall monitoring of a critically ill patient.[1-3] The degree of respiratory monitoring and the number of parameters monitored, depend on the nature of the critical illness. Close monitoring of the respiratory system is particularly essential in respiratory emergencies and in acute respiratory failure, problems so frequently encountered in busy intensive care units. Since the heart and lung function as a single interrelated unit, hemodynamic monitoring is often equally essential in these patients. Acute respiratory failure particularly when due to acute lung injury [acute respiratory distress syndrome (ARDS)] is often complicated by renal dysfunction. Monitoring renal function in these patients is essential for diagnosis and management.

Respiratory monitoring helps: (1) in assessment of respiratory function; (2) in detecting complications involving the respiratory system in the course of any critical illness and (3) in detecting complications of mechanical ventilation. The information provided by this monitoring improves decision-making ability, and hopefully should improve patient outcome. Monitoring techniques can also help to assess progression or regression of pulmonary disease, and the response to various therapeutic interventions. It is however important to bear in mind that decision making in the management of patients with acute respiratory problems should not rest solely on monitoring of the respiratory parameters. Decision making should also depend on overall patient assessment, particularly of the hemodynamic state and of renal function.

MONITORING TECHNIQUES

Monitoring techniques particularly in poor developing countries should always invoke cost-benefit considerations. The potential risk and hazard of invasive monitoring procedures together with the added cost and added patient discomfort should be balanced against the possible benefit of improved diagnosis and better management.

The simplest, most basic and perhaps the most valuable aspect of patient monitoring is the close observation of the patient by the medical and nursing staff. Physical examination and radiological examination from day-to-day are of critical importance and provide a wealth of information. Sophisticated units unfortunately tend to neglect these basic, irreplaceable tenets of critical respiratory care. *All other monitoring techniques should supplement these basic tenets; they should never supplant them.*

An overall complete *physical examination* is of paramount importance. Special emphasis is placed on the heart rate, blood pressure, respiratory rate, examination of the chest and heart. A *radiological examination* of the chest is really a necessary appendage of the physical examination and merits equal importance. *Other basic monitoring techniques* include an arterial pH and blood gas analysis, electrocardiogram (ECG) monitoring, monitoring of hemoglobin and hematocrit, monitoring of urine output and of basic renal function parameters.

Other specific respiratory and hemodynamic parameters may need to be monitored at the bedside depending on the nature of the problem. These include tidal volume (V_T), minute ventilation (V_E), maximum inspiratory force, the

Box 1: Bedside measurements in patients with acute respiratory failure

- Physical examination—heart rate, blood pressure, respiratory rate, clinical examination of the heart and chest
- Radiological examination and ultrasonography of the chest
- Electrocardiogram (ECG) monitoring
- Monitoring of arterial pH, arterial blood gas analysis, oxygenation indices
- Pulse oximetry
- Airway CO_2 monitoring
- Monitoring of renal function
- Monitoring of hemoglobin and hematocrit
- Monitoring of respiratory parameters—tidal volume (V_T), respiratory rate, minute ventilation, maximum inspiratory force, physiological dead space (V_D), V_D/V_T ratio
- Bedside measurement of lung mechanics—dynamic and static compliances, airways resistance
- Monitoring waveform and loop analysis in mechanically ventilated patients
- Measurement of physiologic shunt, oxygen delivery or transport, oxygen consumption
- Monitoring of mixed venous oxygen tension and mixed venous oxygen saturation
- Hemodynamic monitoring in selected cases

physiological dead space (V_D) and the V_D/V_T ratio. Patients on mechanical ventilation may need bedside measurements of lung mechanics—this includes measurements of dynamic compliance, static compliance and resistance to airflow. Physiological shunt (Q_S/Q_T) may also need to be measured together with measurements of oxygen (O_2) delivery or transport (DO_2), and O_2 consumption ($\dot{V}O_2$). Hemodynamic monitoring is essential in some patients; it provides a measure of the cardiac index, filling pressures of the right and left heart, the vascular resistances in the pulmonary and systemic circulation. It also enables measurements of the mixed venous oxygen tension (PvO_2) and saturation, and enables the computing of the shunt equation and of DO_2 and the $\dot{V}O_2$. Finally, an analysis of expired gas, particularly with reference to carbon dioxide (CO_2), may provide useful information in a few patients. Box 1 lists bedside measurements, which are useful in patients with acute respiratory failure.

Not all measurements are necessary in every patient. The clinician should selectively monitor those parameters which are of help either in diagnosis, in management, or in both, bearing in mind the cost-benefit ratio of each monitoring technique in a given patient.

Physical Examination[4,5]

Tachycardia or bradycardia should be assessed in relation to the overall clinical situation. Both can occur in relation to increasing hypoxia.

Changes in arterial blood pressure may be due to several factors. These include hypoxia, hypercapnia, changes in effective circulating blood volume, and changes in cardiac contractility and in systemic vascular resistance due to various causes. Methods of measurement of arterial blood pressure have already been discussed in the earlier Chapter Cardiac Monitoring in Adults.

Respiratory Rate

A careful count and monitoring of the respiratory rate is of crucial importance. The normal range is from 10 to 16 per minute. A rate above 20 per minute always demands a satisfactory explanation. Rates greater than 30 per minute signify respiratory distress and may cause significant hypocapnia.

An increase in the respiratory rate is an early feature of a fall in PaO_2 or a rise in $PaCO_2$. Pulmonary problems producing tachypnea include atelectasis, pneumonia and pulmonary edema. Pleural effusion and pneumothorax should also be carefully excluded. In a critical care setting, sudden tachypnea may also be an early sign of sepsis, of increasing liver cell dysfunction or of pulmonary embolism. Metabolic acidosis initially produces an increase in the depth of breathing followed by an increase in the rate. Increase in respiratory rate and V_E are observed in patients on total parenteral nutrition who receive large carbohydrate loads. A large carbohydrate intake increases CO_2 production (VCO_2) so that a higher V_E is required to excrete the excess CO_2. In a critically ill patient, this constitutes a significant stress demanding increased respiratory muscle work. Respiratory muscle fatigue can result, particularly in patients who already have chronic airways obstruction. Overfeeding with carbohydrates may make weaning (in a patient on mechanical ventilation) impossible, and this is manifested by tachypnea and dyspnea on a T-tube. Decreasing total caloric intake and increasing the ratio of fat: carbohydrate intake decreases the VCO_2 and remedies the situation.

Clinical Examination of the Chest

The degree of chest movements during breathing often enables an astute observer to assess the adequacy of ventilation. Movements may however be deceptive in that adequate chest movement on clinical examination, may still be associated with alveolar hypoventilation, particularly when the physiological V_D is increased.

Asymmetrical movements with diminished breath sounds over the poorly moving side indicate pneumothorax, pleural effusion, pneumonia, atelectasis or uneven ventilation due to right main stem bronchial intubation.

Clinical examination should include a search for signs of respiratory muscle fatigue (see Chapter Acute Respiratory Failure in Adults). A stony dull note over the base of the chest may confirm a doubtful radiological opacity to be related to fluid, rather than to a parenchymal lung lesion.

Auscultation should determine the intensity of breath sounds, character of breath sounds and the presence of wheezes or crackles. Auscultation over the trachea may help in the detection of an inadequately inflated cuff of an endotracheal or tracheostomy tube.

Clinical Examination of the Cardiovascular System

This should be meticulous. Myocardial dysfunction may manifest with a diastolic gallop. A low cardiac output causing a low PaO_2 may be related to pump dysfunction or to mechanical problems like a valvular defect, or a ruptured septum or ruptured papillary muscle.

Radiological Examination

This as mentioned earlier is an appendage or a continuation of a physical examination. A radiological examination helps: (1) to check the position of various tubes, lines, catheters; (2) to detect early pulmonary edema, atelectasis, pneumonia, pleural effusion; (3) to diagnose a pneumothorax, which has been missed, or is undetectable on clinical examination; (4) to detect localized hyperinflation of a portion of the lung due to uneven lung compliance in patients on mechanical ventilation and positive end-expiratory pressure (PEEP); (5) to detect other features of barotrauma and (6) to detect abnormalities in the cardiac silhouette.

Pneumothorax may be difficult to diagnose when only supine films are available for interpretation. Features which may help in diagnosis in such situations include: (1) a sharp curvilinear change in density over the upper quadrant of the abdomen, which becomes significantly radiolucent and (2) a deep lateral costophrenic angle on the affected side.[6,7] A cross-table lateral or decubitus film in the above circumstance should be able to confirm the diagnosis of a pneumothorax.

A bedside ultrasound examination of the chest is extremely useful to confirm or detect fluid within the pleural space.

ECG Monitoring

Arrhythmias are frequent in patients with acute respiratory failure. Supraventricular tachycardia, chaotic atrial tachycardia, atrial flutter/fibrillation all occur. Ventricular rhythm disturbances including ventricular tachycardia may be observed with increasing hypoxia particularly in patients with ischemic heart disease.[8] ECG monitoring techniques have been discussed in an earlier chapter.

Arterial pH and Arterial Blood Gas Analysis

A close monitoring of arterial pH and arterial blood gases is indispensable in the management of acute respiratory failure, as also in the management of any critically ill individual with multiple organ system dysfunction. The PaO_2 is an index of arterial oxygenation, and the $PaCO_2$ is an index of alveolar ventilation. The significance of a low PaO_2 and of changes in $PaCO_2$ have been discussed in the Chapter of Basic Cardiorespiratory Physiology in the Intensive Care Unit, as also in the Chapters Acute Respiratory Failure in Adults and Mechanical Ventilation in the Critically Ill.

It is however extremely important to restress that a fall in PaO_2 in a critically ill patient could be due to either deteriorating pulmonary function or to nonpulmonary causes—in particular to deteriorating cardiovascular function.

The PaO_2/fractional inspired oxygen (FiO_2) ratio is a good overall index of gas exchange.[9] In a similar fashion, the arterial O_2 tension divided by the alveolar O_2 tension (the a/A ratio) remains stable with a varying FiO_2 and is a reliable index of factors governing gas exchange.[9] The normal a/A ratio is greater than 0.75. The ratio can predict the new PaO_2 that should result from a change in O_2 concentration.[10] It is therefore a good pointer to a change in lung function when the FiO_2 administered to the patient is changed.

Pulse Oximetry

In critically ill patients, the PaO_2 might fluctuate significantly, and a sharp fall in the PaO_2 may be missed during suctioning, during change in posture and following the administration of drugs. Continuous monitoring of PaO_2 by special electrodes in the radial, brachial and femoral arteries, as also of mixed venous blood (PvO_2) in the pulmonary artery can be done.[11] These are invasive, expensive techniques and it is doubtful if they help to significantly decrease the morbidity and mortality of very ill patients. However, a universally accepted noninvasive method of measuring arterial O_2 saturation is by the use of the pulse oximeter.[12,13] A beam of light of appropriate wavelength is made to shine through a finger or earlobe. The change in light absorption as blood traverses the vascular bed from beat-to-beat is dependent on the oxyhemoglobin saturation, and this saturation is continuously displayed on the monitor. The sensor, however, needs to be in continuous contact with the finger or the earlobe to which it is clipped. Monitoring O_2 saturation through pulse oximetry is today universally practiced in all critical care units, emergency departments and operation theaters. Pulse oximetry is also used during all minor procedures. A sharp fall in O_2 saturation should alert the physician or surgeon to potential disaster. There are however certain issues which need to be considered in this monitoring technique. Pulse oximetry is fairly accurate in the range of mild to moderate hypoxia. When hypoxemia is severe, as with a fall in O_2 saturation below 75%, its accuracy is suspect. In severe hypoxemia, the difference between measured O_2 saturation and the O_2 saturation obtained through pulse oximetry ranges from 5% to 12%.

Pulse oximetry is also unreliable in patients with severe hypotension and in patients with poor perfusion of the peripheries either from shock due to any etiology or from the use of vasopressors causing severe vasoconstriction. These factors impair blood flow to the site of the sensor of the oximeter and cause a variation in the contour and intensity of the pulse beats used to calculate O_2 saturation. Most oximeters are devised and programmed to stop recording O_2 saturation in states of low perfusion or when a poor pulse

signal is being measured. However, some oximeters continue to display O_2 saturation in spite of marked hypoperfusion and hypotension. These results are inaccurate, and the O_2 saturation readings under the above circumstances are misleadingly high.

Pulse oximetry though of great use in critical care medicine cannot and should not replace measurement of arterial blood gases. The measurement of PaO_2, pH remains of vital importance. The PaO_2 cannot always be accurately predicted from the O_2 saturation readings of the oximeter. When the O_2 saturation is between 95% and 100%, the exact measure of the PaO_2 can only be made by an accurate blood gas (PaO_2) estimation.

Clinical Uses

- Monitoring O_2 saturation in all procedures—major and minor. Minor procedures would include bronchoscopy, endoscopies, hemodialysis, cardioversion, injection of dyes and contrasts for imaging purposes.
- Keeping track on patients who are hypoxemic.
- Helping in ventilator support, as it enables (1) adjustment of FiO_2 as per the O_2 saturation readings and (2) detection of effects on arterial oxygenation with different modes of ventilator support and with use of PEEP.
- Aiding the weaning process, as it tracks the O_2 saturation when the patient is off ventilator support.

It is to be noted that the pulse oximeter cannot measure carboxyhemoglobin nor measure oxyhemoglobin in the presence of carboxyhemoglobin. Unreliable readings are also observed in methemoglobinemia.

Transcutaneous blood gas analysis is an important non-invasive method of monitoring infants with acute respiratory failure, and has been described in the Chapter Respiratory and Hemodynamic Monitoring in Children.

Airway CO_2 Monitoring

Airway CO_2 monitoring is done noninvasively, either with a quickly responding infrared CO_2 analyzer or a mass spectrometer, which measures CO_2 directly at the end of the endotracheal tube. Breath-by-breath analysis of the end-tidal PCO_2 ($PETCO_2$) can thus be obtained from an endotracheal tube during mechanical ventilation. Nonintubated patients can have the $PETCO_2$ sampled by a catheter placed through the nares in the posterior nasopharynx. Continuous waveforms can be recorded by capnography and the expired CO_2 is thereby monitored. The end-tidal pressure of CO_2 is related to partial pressure of alveolar CO_2 ($PACO_2$), which in turn is a measure of the $PaCO_2$. Thus, when expired CO_2 waveforms are continuously monitored, an estimate of the $PETCO_2$ would amount to a noninvasive measurement of the $PaCO_2$. The $PETCO_2$ will be increased if there is alveolar hypoventilation, or an increase in the VCO_2; it will be decreased if there is alveolar hyperventilation.

Analysis of the $PETCO_2$ thus helps in assessing the adequacy of alveolar ventilation, and guides ventilator adjustments to ensure that this is achieved. However, the close correlation between $PETCO_2$ and $PaCO_2$ observed in normal subjects does not always hold in patients with marked ventilation/perfusion (V/Q) abnormalities. In such patients, there is a divergence between $PETCO_2$ and $PaCO_2$ values. The expired gas in the presence of a V/Q abnormality is more influenced by lung units with high V/Q ratios and increased V_D, whereas the arterial blood is more weighted by lung units with low V/Q ratios and increased shunt. The $PETCO_2$ is thus an unreliable estimate of the $PaCO_2$ in these circumstances, though monitoring of changing trends may still be of use.

Capnography and $PETCO_2$ monitoring have been useful in the following other clinical situations—

- To provide a noninvasive method determining correct endotracheal tube placement. The capnograph should display an increased CO_2 concentration during expiration and the $PETCO_2$ reading should be plausible.
- To assess the efficacy of cardiopulmonary resuscitation. A very low $PETCO_2$ during cardiopulmonary resuscitation points to a very poor return of venous blood to the right heart and central circulation.

Monitoring Renal Function

Renal function needs to be monitored in every critically ill individual. *Close monitoring is especially important in acute respiratory failure, as renal dysfunction is a frequent complication and this significantly adds to the mortality*. Sweet et al.[14] in a study of 400 critically ill patients noted a mortality of 32% in respiratory failure alone, 44% in renal failure alone and 65% in combined respiratory and renal failure. Hypoxemia, acidosis, mechanical ventilation and use of PEEP may all disturb renal hemodynamics and tubular functions. Sepsis, hypovolemia and the use of nephrotoxic drugs can also significantly add to renal dysfunction.

Urine output, blood creatinine, blood urea nitrogen and serum electrolytes require close monitoring. A urine sodium level less than 10–20 mEq/L or a urine osmolality greater than 600 mOsmol/L suggests hypovolemia.

Renal function can also be monitored by measuring the urine osmolality, the plasma osmolality and the osmolar clearance (COsm). The urine osmolality divided by the plasma osmolality is calculated; if greater than 1.7 the concentrating ability of the kidney is good.

The COsm is calculated as follows—

$$\text{Osmolar clearance} = \frac{\text{Urine osmolality}}{\text{Plasma osmolality}} \times \text{Urine output}$$

The normal COsm is 120 mL/hour; it is decreased in renal dysfunction.

The normal calculated serum osmolality is between 275 mOsmol/L and 295 mOsmol/L (see Chapter Fluid and Electrolyte Disturbances in the Critically Ill). The calculated osmolality is 5–8 mOsmol less than the measured osmolality, the difference being related to anions like phosphate and

lactate. The greater this difference between measured and calculated osmolality in a critically ill patient with acute respiratory failure, and the greater the increase in serum lactic acid, the poorer the prognosis.

Monitoring Hemoglobin and Hematocrit

Monitoring hemoglobin concentration is essential as O_2 content of the blood depends significantly on this parameter. It is best to keep the hemoglobin concentration around 11 g/dL. The hematocrit is affected by a loss or gain in the red blood cells or in plasma volume. Sudden blood loss will not immediately change either hemoglobin or hematocrit. The hematocrit falls gradually as a result of shift of fluid from the interstitial compartment into the vascular compartment. This is a compensatory mechanism, which helps to maintain an effective circulating volume. Blood loss of 500 mL is replaced by fluid from the interstitial compartment initially at a rate of 1 mL/min.[15] The hematocrit needs to be monitored periodically; following hemorrhage, it needs to be monitored every 4–6 hours.

Monitoring Specific Respiratory and Hemodynamic Parameters

Tidal Volume, Respiratory Rate, Minute Ventilation and Maximal Inspiratory Force

Bedside spirometers, as also dry gas meters, are easily available to measure exhaled volumes. V_T, respiratory frequency (f) and V_E often need to be monitored, particularly in ventilatory failure and in patients who are to be weaned off ventilator support. As mentioned earlier, an increase in respiratory rate (f) may be the first sign of respiratory distress, and the degree of rise is proportional to the severity of underlying lung disease. Rapid shallow breathing is commonly observed in those who fail to be weaned from ventilator support. This can be quantitated by the ratio of f/V_T; if the value is above 100 breaths per minute per liter weaning is generally unsuccessful.[16]

A rapid respiratory rate with a low V_T may cause a fall in alveolar ventilation, particularly if the V_D is increased. A marked increase in V_E should lead to hypocapnia; if the $PaCO_2$ is within normal limits, it points to a marked increase in V_D. A V_T greater than 5 mL/kg and a vital capacity (VC) greater than 10 mL/kg suggest a good chance of weaning the patient from ventilator support. A V_E greater than or equal to 10 mL makes weaning difficult and unlikely. A maximum inspiratory force less than –20 cm H_2O generally necessitates the use of mechanical ventilatory support (see Chapter Mechanical Ventilation in the Critically Ill).

Physiological Dead Space

As explained in the Chapter Basic Cardiorespiratory Physiology in the Intensive Care Unit, an increase in physiological V_D points to wasted ventilation. Mechanical ventilation by itself leads to an increase in V_D. In respiratory failure and in many pulmonary pathologies, an increase in V_D is due to increased ventilation of alveoli, which are poorly perfused or unperfused.

$$\frac{V_D}{V_T} = \frac{PaCO_2 - P_ECO_2}{PaCO_2}$$

where P_ECO_2 in the mixed expired CO_2 tension.

If the $PETCO_2$ is substituted for $PaCO_2$, anatomical V_D can be calculated by analysis of the expired gas. An increase in V_D or in the V_D/V_T ratio in acute respiratory failure due to severe lung injury (ARDS) correlates with an increase in mortality. The higher the V_D, the greater the mortality.[17]

Bedside Measurement of Lung Mechanics

It is important to monitor lung mechanics in patients on ventilator support. The volume delivered by the ventilator divided by the peak airway pressure, constitutes the dynamic compliance. It includes the components of resistance to airflow and resistance related to the elastic properties of the lung.

$$\text{Dynamic compliance} = \frac{\text{Tidal volume}}{\text{Peak pressure}}$$

If PEEP is being used or if auto-PEEP is present, then

$$\text{Dynamic compliance} = \frac{\text{Tidal volume}}{\text{Peak pressure} - \text{PEEP (if present)}}$$

Dynamic compliance correlates with changes in airway resistance.

If we occlude the outflow of the ventilator momentarily (by turning the knob to inspiratory hold or to pause), the pressure dial will show a momentary drop at which no airflow occurs. This pressure is the plateau pressure.

$$\text{Static compliance} = \frac{\text{Tidal volume}}{\text{Plateau pressure} - \text{PEEP (if present)}}$$

Static compliance correlates with changes in elastic recoil.

The normal static compliance of the lung and the chest wall in mechanically ventilated patients is 70 mL/cm H_2O. When the static compliance of the lung and the chest wall is less than 20 mL/cm H_2O, the lungs are very stiff, and the degree of respiratory failure is invariably severe. In very severe acute lung injury, the static compliance may be as low as 10 mL/cm H_2O.

Periodic monitoring of the peak inflation pressure and plateau pressure for a fixed V_T, thus gives a good indication of lung mechanics. High plateau and peak pressures, and in particular progressively increasing plateau and peak pressures, are indicative of increasingly stiff lungs. This occurs in pulmonary edema, atelectasis, pneumonia, acute lung injury and pneumothorax. It is also observed when for some reason the patient strongly clashes with the machine.

Normally the peak pressure exceeds the plateau pressure by less than 5 cm H_2O. If the plateau pressure is significantly

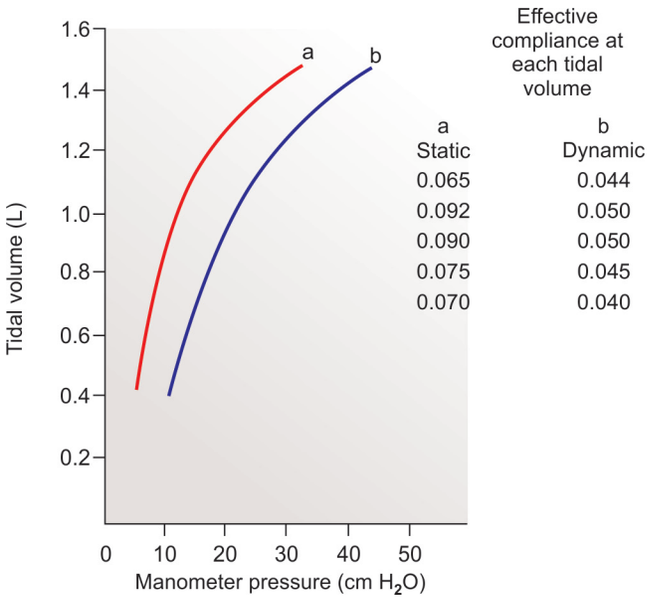


Fig. 1: Effective static and dynamic compliance curves calculated at varying tidal volumes: (a) effective static compliance curve; (b) effective dynamic compliance curve. Figures show effective (a) static and (b) dynamic compliance at each tidal volume

Source: Modified from Bone RC. Adult Respiratory Distress Medicine. New York: Thieme Medical Publishers; 1981.

lower than the peak pressure, it indicates an increase in airways resistance (Raw). A normal plateau pressure with a markedly increased peak pressure points to a marked increase in Raw. This can be due to a blocked endotracheal or tracheostomy tube, to secretions within the bronchial tubes or to bronchospasm (see Chapter Mechanical Ventilation in the Critically Ill). If airflow is measured, Raw can be calculated as follows—

$$\text{Raw} = \frac{P_P - P_{ST}}{V}$$

where P_P is the peak pressure, P_{ST} is the static or plateau pressure, V is the volume of airflow measured at end-inspiration at the time of peak pressure. In normal subjects, Raw is between 2 cm H_2O/L/sec and 3 cm H_2O/L/sec. In severe airways obstruction, Raw may be more than 10 times the normal value.

It is sometimes important to chart on a graph the dynamic and static compliance of the lungs, by ventilating the lungs at different V_{Ts} and recording the peak and plateau pressures for each volume. The dynamic compliance curve correlates with Raw and the static compliance curve with lung stiffness. The method of charting compliance is as follows—

- Select different V_{Ts}—400, 600, 800, 1,000, 1,200 mL.
- For each volume record spirometer volume, peak pressure, plateau pressure (ensure that the tracheostomy cuff is adequately inflated and that there is no air leak).
- Calculate dynamic compliance and static compliance as explained earlier.
- This procedure is repeated for each volume setting.
- If at any volume setting, the peak pressure shows a marked increase, a further increase in V_T setting should not be done as barotrauma may result.
- The data is charted on a graph so that dynamic and static compliance curves are obtained for varying V_{Ts} (Fig. 1).

Peak and plateau pressures (with graphs of dynamic and static compliance) can also be charted at a constant V_T with a gradual increase in PEEP. At high V_{Ts} or with higher PEEP levels, decreasing static compliance signals hyperinflation and care must be taken to avoid barotrauma. The incidence of the latter increases with high V_{Ts} or high levels of PEEP, which causes overdistension of the alveoli.

A careful examination of the static and dynamic compliance curves provides further information on lung mechanics (Figs 2A to C). Conditions causing an increase in Raw, shift the dynamic compliance curve to the right and flatten it. Conditions causing increasingly stiff lungs or causing chest wall stiffness, shift both the static and dynamic compliance curves to the right and flatten both.[18] If the patient has a low PaO_2 and both compliance curves are unchanged, the possibility of pulmonary embolism should be entertained.[15]

The charting of compliance graphs is subject to two possible errors.[15] If the patient clashes with and resists the ventilator, the pressure required to inflate the lungs will be greater than when he is relaxed. Also, if the patient actively assists the ventilator in inspiration, the pressure shown on the ventilator dial will be less than the total pressure required.

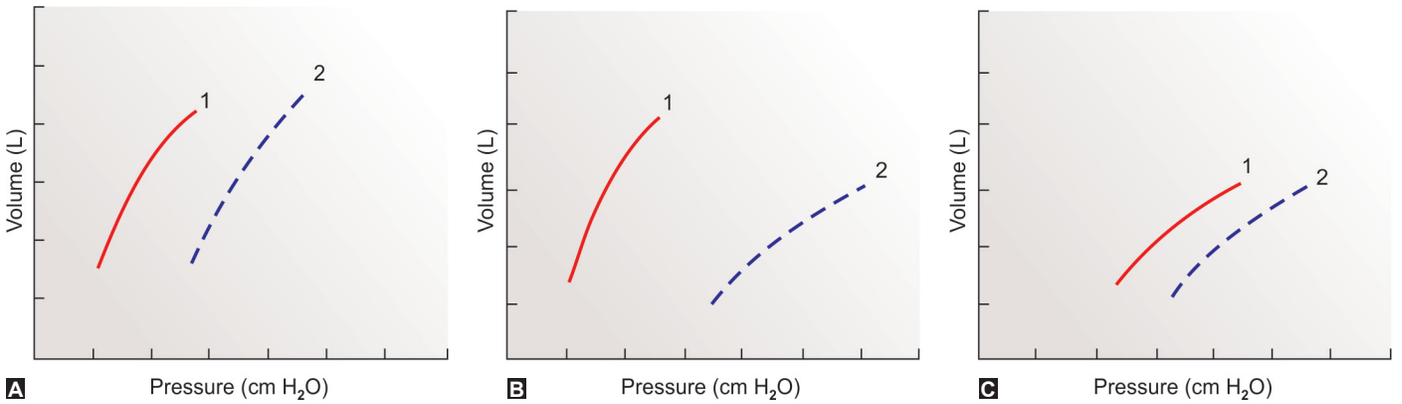
Ordinarily compliance curve charts are rarely necessary, and mere monitoring of peak and plateau pressures in relation to V_T settings provides adequate information on lung mechanics in patients on ventilator support.

Intrinsic Positive End-Expiratory Pressure

Intrinsic PEEP (auto-PEEP) is dealt with at length in the Chapter Mechanical Ventilation in the Critically Ill. Intrinsic PEEP is measured in relaxed patients on ventilator support by using the expiratory hold maneuver at the end of expiration. Intrinsic PEEP imposes an increase in the respiratory threshold load; this needs to be overcome by an increased inspiratory muscle effort so that a sufficient negative pressure is created in the central airways to trigger the ventilator. The inspiratory effort needed to trigger the machine must overcome the set sensitivity plus the intrinsic PEEP. Monitoring intrinsic PEEP is important not only in ventilated patients who have airways obstruction, but also in patients with other lung pathologies such as acute lung injury.

Waveform and Loop Analysis in Mechanically Ventilated Patients

Modern ventilators are provided with gadgetry capable of displaying breath-by-breath waveforms, pressure volume loops and also flow volume loops. The waveforms provided are the pressure-time waveform, the volume-time waveform and the flow-time waveform. Analysis of waveforms and loops enables the clinician to determine changes in resistance



Figs 2A to C: (A) Static compliance curve (1) and dynamic compliance curve (2) in normal individuals. These curves remain unchanged in patients who are hypoxic due to pulmonary embolism. (B) Static (1) and dynamic (2) compliance curves in patients with increased airway resistance. Note flattening and shift of the dynamic compliance curve (2) to the right. (C) Static (1) and dynamic (2) compliance curves in patients with increased stiffness of the lungs. Note that both the static and dynamic compliance curves are flattened and shifted to the right

and compliance of the patient's lungs while on ventilator support. A correct interpretation of waveforms and loops allows the intensivist to make a correct clinical decision on patient-ventilator relationship. It is our considered opinion that the display of waveforms and loops is of help; yet patient management can be as good and as effective with good clinical observation coupled with basic monitoring of respiratory mechanics discussed earlier.[19]

Physiological Shunt

The true venous admixture is an index of the quantity of cardiac output perfusing unventilated alveoli. This has already been explained in the Chapter Basic Cardiorespiratory Physiology in the Intensive Care Unit.

$$\frac{Q_S}{Q_T} = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}$$

where Q_S is the shunt, Q_T is the total blood flow to the lungs, and CcO_2, CaO_2 and CvO_2 refer respectively to the O_2 content of pulmonary capillary, arterial and mixed venous blood.

Shunt is measured while breathing 100% O_2 for 20 minutes. If inadequate time is given to wash out all nitrogen from poorly ventilating alveoli, the degree of shunt will be overestimated. On the other hand, prolonged breathing of 100% O_2 promotes atelectasis and increases the Q_S/Q_T value.

If the shunt is measured on an FiO_2 of less than 1, ventilation-perfusion inequalities will contribute to the shunt. It needs to be stressed that a change in the degree of shunt may reflect either a change in pulmonary function influencing gas exchange or may be related to a change in cardiac output. A decrease in the cardiac output in acute lung injury can decrease the shunt within the lungs and thereby cause a rise in the PaO_2. A decrease in cardiac output, on the other hand, could lower the PvO_2 and thereby further decrease the PaO_2. The final effect on the PaO_2 depends on which of the above two hemodynamic changes predominates.

Oxygen Delivery

The importance of DO_2 has been dealt with in a number of chapters.

$$\text{Oxygen delivery} = \text{Cardiac output} \times CaO_2$$

where CaO_2 is the content of arterial O_2 (see Chapter Basic Cardiorespiratory Physiology in the Critical Care Unit).

Monitoring Mixed Venous Oxygen Tension and Mixed Venous Oxygen Saturation

The $P\bar{v}O_2$ and mixed venous oxygen saturation ($S\bar{v}O_2$) are often used as indices of tissue oxygenation and of cardiac output. This can only be possible if a pulmonary artery catheter is in use. Fiberoptic catheters are available for continuous monitoring of $S\bar{v}O_2$. A $P\bar{v}O_2$ less than 30 mm Hg invariably signifies severe hypoxia due to poor tissue perfusion. It is generally accepted that though the $P\bar{v}O_2$ accurately reflects tissue oxygenation in hemorrhagic and hypoxic shock, it often does not do so in septic shock and in patients with acute lung injury (ARDS). Misleadingly high $P\bar{v}O_2$ values may be obtained in these situations even when there is marked tissue hypoxia and lactic acid acidosis. This is probably related to a number of factors, chiefly perhaps to inability of the tissue cells to utilize O_2.[20]

Measuring $P\bar{v}O_2$ and $S\bar{v}O_2$ requires invasive hemodynamic monitoring. In most instances, O_2 saturation in the superior vena cava ($Sc\bar{v}O_2$) is measured in place of $P\bar{v}O_2$ and $S\bar{v}O_2$.

The $Sc\bar{v}O_2$ normally measures 65–70% and is 3–5% higher than $S\bar{v}O_2$. The $Sc\bar{v}O_2$ is measured through a catheter in the superior vena cava; the catheter is so designed as to give a continuous display of the $Sc\bar{v}O_2$.

Monitoring Serum Lactate Levels

The normal lactic acid levels in blood are less than or equal to 2 mm/L. Increase in serum lactic acid levels indicates tissue hypoxia. A normal or even an increased DO_2 may however at times be associated with increase in lactic acid levels. This either indicates that the O_2 needs of the tissues are still relatively greater than the O_2 delivered to the tissues or that the tissues are unable to effectively utilize O_2 (see Section Clinical Shock Syndromes).

Hemodynamic Monitoring

This is indicated in select cases of acute respiratory failure. A stable cardiovascular function is essential for good respiratory function, the heart and lungs being inseparably linked in function. Hemodynamic monitoring is invasive, and should be done with circumspection after due consideration of potential risks versus the possible benefits. It is particularly helpful in acute lung injury as it enables the clinician to manipulate filling pressures and adjust inotropic support so that DO_2 to tissues is adequately maintained.

Computer Monitoring[21]

We have no experience with the mass spectrometer and of online simultaneous measurements of gas exchange and lung mechanics. The cost-effectiveness of this technology is doubtful, perhaps confusing, and at times unreliable. The data obtained does not substantially add to patient management and may well detract from it. More time may be spent in looking at computer data rather than in observing the patient. This is not to decry the use of computers; it is a plea to use them in a proper perspective particularly in poor countries.

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SECTION

5

Imaging in the Critical Care Unit

- Introduction
- Imaging Techniques in the Chest
- Imaging Techniques in the Abdomen
- Neuroimaging Techniques

CHAPTER 9

Introduction

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Imaging procedures are extremely useful in the diagnosis and management of acute illnesses in the critical care unit. Therapeutic interventions using image guidance are being increasingly practised in selected problems, thereby considerably reducing both morbidity and mortality. Numerous imaging modalities are now available for diagnostic and therapeutic help. These include radiology, ultrasonography, echocardiography, computed tomography (CT scanning), magnetic resonance imaging (MRI), nuclear scintigraphy, Doppler study of blood flow through the arteries and veins, angiography and digital subtraction angiography (DSA). It is important for the critical care physician to be aware of the advantages, disadvantages, benefits, risks and complications of each of these modalities. The mode or modes selected in a particular patient should thus increase the diagnostic and therapeutic yield at minimal cost. Cost is indeed an extremely important factor to be considered in our country. CT scans and MRI are expensive imaging procedures. To repeat them unnecessarily in a critically ill individual is bad medicine.

Management of critically ill patients requires a close liaison and communication between the radiologist and the critical care physician. Good management would also entail early availability of results of imaging procedures. This entails rapid processing of images, immediate interpretation by the radiologist, and prompt availability of the films to the clinician. A daily discussion between the radiologist and the intensive care unit physician of all X-rays and other imaging procedures is mandatory for the smooth, efficient functioning of a critical care unit.

Some imaging procedures like X-rays of the chest and abdomen, ultrasonography, echocardiography, and Doppler studies, can be performed at the bedside. Other investigations like CT scan, MRI, angiography, nuclear scintigraphy, unfortunately require the patient to be transported to the imaging department within the hospital. The risk of transfer of a critically ill individual to other departments, even if within the hospital, should be carefully assessed. All necessary safeguards and precautions must be ensured, and the risk-benefit ratio carefully considered before transfer.

The next chapter deals with imaging of the chest, followed by imaging of the abdomen and of the central nervous system. The imaging modalities considered are radiology, ultrasonography, CT and MRI. Echocardiography, Doppler studies, angiographic studies and nuclear scintigraphy are briefly discussed in relation to the relevant clinical problems in different chapters of this book. Nuclear scintigraphy is the one modality, which has been infrequently used by our unit. This is because of logistic reasons: we do not have a nuclear medicine department, and the use of nuclear medicine would necessitate transfer of seriously ill patients to centers outside the hospital. Nuclear scintigraphy does however have important uses in the critically ill individual. These include: myocardial perfusion scanning in cardiac disease, evaluation of an occult gastrointestinal bleed, establishing the diagnosis of acute cholecystitis, and the localization of an occult infection.

It needs to be stressed that imaging procedures for diagnosis and management in a critically ill individual, should supplement and never supplant a good clinical examination.

A machine, particularly an expensive one, does not have to be used just because it is available. It should be used only when its use confers a clear benefit to the patient, and not merely to the institution which houses it.

CHAPTER 10

Imaging Techniques in the Chest

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GENERAL CONSIDERATIONS

Radiology plays a key role in the successful management of critically ill patients. The chest radiograph, especially when performed at the bedside is an invaluable examination in identifying and evaluating pulmonary and cardiac problems.

It is often debated whether there is a need for daily chest radiographs or only stat films. Many studies have shown that daily portable chest X-rays are very effective in diagnosing unexpected problems resulting in treatment alterations, which in turn affect the final outcome of the patient.[1-3] The quality of portable chest X-rays however is a factor of major concern. The limited power output and longer exposure time required for portable chest X-rays results in poorer quality than departmental films. There are other factors, which also contribute to non-consistent quality. In a large hospital with numerous radiographers, many different film screen combinations and multiple portable X-ray machines, the quality of portable films is bound to be inconsistent as each radiographer uses technical factors, which he feels are appropriate. Similarly, film screen combinations and portable machines require different settings. The ideal situation is for a single radiographer to use a single film screen combination and a single portable machine to take all the radiographs in the intensive care unit (ICU), as this would eliminate the variations. Often in a large hospital, this is not possible. For this reason, it is advocated that the radiographer should note the radiographic factors used, the distance, the film screen combination and the portable machine used, on the film. As films are taken on a daily basis, the radiographer taking the next X-ray can view the previous day's films, note the factors and other technical details and repeat the same, so that there is no change in the consistency of the radiographs. In addition, if the previous day's films were overexposed or underexposed, then the factors can be adjusted to achieve optimal quality.

The recent introduction of digital radiography has resulted in a dramatic improvement in image quality of radiographs in the critically ill patient especially at the bedside. Not only is there a marked improvement in image quality, but also there is no need for retakes. The images being digital can be adjusted to correct any under or overexposure, thus helping to remove any variability. There are two means to go to digital. One is to have purely digital portable X-ray machines, these are very expensive, and the other is to use a portable digital detector with routine portable X-ray machines. Rather than recording the image on a film, the image is recorded on a digital detector as pixels. There are two types of detectors available: computed radiography and digital. The computed radiography detector needs to be brought back to the imaging department to be read and erased. In case of digital detector, the image is available instantly at the bedside. This is a significant advantage in addition to better image quality over the computed radiography detectors.

Most of the X-rays taken in the ICU are an AP view with the patient upright. In this view, there is cardiac magnification, and it is very difficult to comment on the cardiac size. It should also be kept in mind that in supine chest X-rays the lung volume appears smaller. Another point, which is often overlooked, is the difficulty encountered in getting a critically ill patient to sit upright. Pathology in the lung bases can easily be missed in an X-ray chest taken when a patient is not totally upright. Every effort should therefore be made to position the patient correctly.

Computed tomography (CT) scan has evolved over the last two decades and is now an integral part of the radiological work-up. Its cross-sectional display eliminates superimposition

of structures, improves contrast, resolution and tissue characterization, thus allowing better diagnosis of diseases. The only disadvantage is the need to transport the patient to the CT scanner suite and back. This can be time consuming and occasionally risky with the patient away from the ICU. However, the useful information offered by CT far outweighs the risks. In one study, evaluation of thoracic CT in critically ill patients provided useful additional information, which was not available on plain chest X-rays in 70% of the cases.[4,5]

PULMONARY EDEMA

This is one of the most important pathologies affecting the cardiovascular system and a very frequent cause of respiratory distress in the critically ill patient. There are three main causes for pulmonary edema: (1) cardiogenic edema; (2) overhydration edema due to over-infusion of fluids or renal failure; and (3) increased capillary permeability due to various insults to the capillary membrane. The initial treatment for pulmonary edema is the same irrespective of the etiology. Management however requires accurate assessment and correction of the underlying cause. The chest radiograph should therefore be evaluated not only for signs of pulmonary edema, but also to identify the underlying etiology.

The radiographic features of pulmonary edema can be considered in three categories—

1. Pulmonary venous hypertension.
2. Interstitial edema.
3. Alveolar edema.

On an upright chest radiograph of a normal subject, the lower lobe vessels are more prominent than the upper lobe vessels. With elevation of pulmonary venous pressures, the blood flow is redirected to the mid and upper zones. In addition, non-perfused blood vessels in the upper zones are opened up, and there is reflex vasoconstriction of the lower zone vessels, resulting in a vascular redistribution on the chest radiograph. The appearances can be classified into three types: (1) normal or caudalization of blood flow, i.e. normal flow patterns; (2) balanced, essentially equal blood flow to apices and bases; (3) inverted or cephalization of blood flow when the upper lobe vessels are larger than the lower lobe vessels. These findings will only be observed on upright X-rays; recumbent or supine X-rays may show no evidence of vascular redistribution.

When the pulmonary capillary wedge pressure (PCWP) increases to 18–25 mm Hg, there is transudation of fluid into the interstitium; when the PCWP is greater than 25 mm Hg, transudation of fluid occurs into the alveoli. Interstitial edema is recognized by the presence of Kerley lines, perivascular cuffing, peribronchial cuffing and perihilar haze. The Kerley lines are of three types: (1) Kerley A lines; (2) Kerley B lines, and (3) Kerley C lines. Kerley A lines are 2–6 cm in length and about 1 mm in thickness. These lines radiate from the hilum to the periphery of the lung and are best seen in the upper zones. Kerley B lines are 1–2 cm long and about 1 mm in diameter. These lines are seen in the subpleural regions of the lower zones adjacent to the costophrenic angles. Kerley B lines are more frequently seen than the Kerley A lines. Kerley C lines are considered as an overlap between Kerley A and B lines. These are not important as they are seldom detected on a chest radiograph. With transudation of the fluid into the interstitium around the vessels and bronchi, the sharp margin of these structures becomes indistinct, and this is known as perivascular and peribronchial cuffing. Similarly, exudation into the interstitium about the hilum results in a perihilar haze.

Alveolar edema occurs with transudation of fluid into the alveoli and is characterized by fluffy ill-defined opacities in the lung, especially in the central zones giving rise to a bat's wing or butterfly appearance. Often an air bronchogram pattern may be seen within these ill-defined fluffy shadows.

Unilateral pulmonary edema is not an uncommon finding and poses a diagnostic dilemma, as the radiological appearances may be similar to those seen with an inflammatory pathology. Pulmonary edema may occur in one lung or lobe, either due to a disease process within that lung (e.g. patients lying on one side for prolonged periods, or unilateral veno-occlusive disease), or may be related to some pathology in the opposite lung, which prevents pulmonary edema from developing on the same side (e.g. cases with unilateral pulmonary emboli or the Swyer-James syndrome). The distribution of unilateral pulmonary edema may be patchy, with some areas of the lung being more affected than others. This is usually due to underlying emphysema, scarring, or radiation injury. It is difficult to differentiate focal pulmonary edema from focal inflammation radiologically, and a clinical correlation together with serial follow-up X-rays is often needed to confirm the diagnosis.

DIFFERENTIATION BETWEEN CARDIOGENIC EDEMA, OVERHYDRATION EDEMA AND CAPILLARY EDEMA

Milne and coworkers[6] have reported that these could be differentiated on the basis of three principal features: (1) distribution of pulmonary blood flow; (2) distribution of pulmonary edema and (3) width of the vascular pedicle. Systemic blood volume is accurately depicted by the vascular pedicle, which is the portion of the superior mediastinum containing the great vessels. As these vessels are distensible, they respond to changes in the circulating blood volume.[7]

It has been found that the vascular pedicle was enlarged in 60% of patients with cardiac edema, and 85% of patients with renal failure or overhydration; in contrast, 70% of patients with capillary permeability edema had a vascular pedicle of normal width.[6] As regards the distribution of pulmonary flow, patients with overhydration edema had balanced or cephalization of blood flow, while patients with capillary permeability edema had normal or balanced flow. The distribution of edema was symmetric, perihilar in patients with cardiac or overhydration edema, whereas capillary permeability edema appeared patchy and peripheral.

ACUTE LUNG INJURY (ACUTE RESPIRATORY DISTRESS SYNDROME)

Acute lung injury [acute respiratory distress syndrome (ARDS)] is a consequence of acute lung injury resulting in damage to the alveolar epithelium and pulmonary vasculature with resultant capillary permeability edema. Three stages have been described in ARDS.[8]

Stage I is the earliest and occurs within a few hours after the insult. Pathologically, there is a pulmonary capillary congestion, endothelial cell swelling and extensive microatelectasis. As the fluid leakage into the interstitium is minimal, the radiograph at this stage shows relatively clear lungs, though the lung volumes may appear small due to diminished compliance. If the acute lung injury is due to primary lung pathology such as aspiration or pneumonia, then pulmonary opacities related to this condition will also be seen.

Stage II occurs about 2–5 days after the injury. The pathological features are of fibrin deposition, hemorrhagic fluid leakage and hyaline membrane formation. These are seen on the radiograph as diffuse ill-defined bilaterally symmetrical patchy areas of consolidation, which may have an air bronchogram pattern present in them. Asymmetrical shadowing can also occur. Rarely, there may be associated pleural effusions, but these are usually small.

Stage III is characterized by collagen deposition, proliferation of fibroblasts and epithelial cells. Radiologically, the appearance is of progressive lung destruction with a transition from alveolar to interstitial opacities. The treatment of ARDS includes positive pressure ventilation, which may result in barotrauma, manifested by pneumothorax, pneumatocele, pneumomediastinum or pulmonary interstitial emphysema. With the use of positive end-expiratory pressure (PEEP), there may be areas of overinflation or barotrauma in the lung parenchyma that give rise to the appearance of disappearing opacities. However, this is not accompanied by evidence of clinical or physiological improvement. After recovery, there may be residual fibrosis and focal emphysema, but often the X-ray returns to normal.

Pneumothorax and pneumomediastinum are easily identified on radiographs. However, CT helps in detecting the early features of barotrauma, e.g. interstitial pulmonary emphysema and pneumatoceles. Interstitial pulmonary emphysema is seen as thin streaks of air in the interstitium and should be differentiated from an air bronchogram. There is sharp delineation of the bronchovascular bundle in interstitial pulmonary emphysema. A CT examination can detect a large pneumatocele formed by the coalescing of small thin walled peripheral cysts.

In stage II ARDS, the X-ray may resemble that of cardiogenic pulmonary edema, and needs to be differentiated from it. In contrast to cardiogenic, uremic and hypervolemic pulmonary edema, the alveolar edema of ARDS is not associated with widening of the vascular pedicle, cardiomegaly or altered pulmonary blood flow distribution. The pulmonary vessels visualized are usually constricted because capillary leak occurs directly into the alveolar spaces and septal lines are absent.

PNEUMONIA

Aspiration Pneumonia

Aspiration pneumonia occurs as a result of endotracheal aspiration of oropharyngeal or gastric secretions. Tracheal and esophageal intubation, depressed cough reflex, impaired mucociliary function, increased secretions, cardiopulmonary resuscitation events and the supine posture are factors that predispose the critically ill patient to aspirate. Radiologically, the demonstration of suddenly appearing new focal pulmonary lesions should raise the suspicion of aspiration. The areas of involvement are mainly in the dependent portion of the lung—superior segments of the lower lobes, or posterior segments of the upper and lower lobes when the patient is supine. If the patient has been in the lateral decubitus position, aspiration causes collapse consolidation of multiple segments of one lung, while the other lung is spared. Patients who are prone in roto beds show involvement of the anterior segments of the upper and lower lobes, the middle lobe and the lingual.[9] Aspiration pneumonia may be complicated by a necrotizing lung abscess. Aspiration of gastric contents results in an acute pulmonary reaction with pulmonary edema causing chemical pneumonitis. This type of pneumonitis may eventually progress to ARDS or secondary bacterial pneumonia.

Nosocomial Pneumonia

Nosocomial pneumonia is defined as a lower respiratory tract infection occurring after 72 hours of hospital admission and is an important cause of death in hospitalized patients. A large study showed that 31% of patients admitted to an ICU were at risk of developing pneumonia following intubation.[10] Radiologically, nosocomial pneumonia is seen as new or worsening multifocal parenchymal opacities. Nosocomial pneumonias are often complicated by a lung abscess or empyema. These complications help to differentiate nosocomial pneumonia from other conditions like atelectasis or pulmonary edema that may present in critically ill individuals as new opacities on a chest radiograph.

Community-Acquired Pneumonia

The appearances can be divided into three types: (1) lobar pneumonia; (2) bronchopneumonia and (3) interstitial pneumonia. In lobar pneumonia, there is usually alveolar inflammation resulting in a diffuse opacity with the presence of an air bronchogram pattern. The opacity usually involves a segment or a portion of a lobe; rarely, it may involve the entire lobe. It is generally impossible on radiographic appearance to differentiate the various bacteriological organisms that cause pneumonia. However, when there is evidence of increased lung volume in the affected portion of the lung, then the possibility of *Klebsiella* or pneumococcal pneumonia should

be considered. It is important to localize the consolidation to a specific lobe, as this is helpful to the bronchoscopist. The silhouette sign is used to determine the site of the consolidation. Whenever the consolidation is adjacent to a soft tissue structure, it causes obliteration of the margin of that structure. When the consolidation is adjacent to the right border of the heart, it is localized to the right middle lobe; when the consolidation is in the left lingula, it obliterates the left heart border. Lower lobe pneumonias may cause loss of the diaphragmatic contour.

Bronchopneumonia results from inflammation of the terminal end-respiratory bronchioles. Radiologically, this is seen as patchy, infiltrates involving multiple segments. There may be evidence of volume loss, but air bronchograms are usually not visualized.

Interstitial pneumonias are usually caused by viruses or *Mycoplasma pneumoniae*. Radiologically, they appear as diffuse reticular opacities in both lung fields with peribronchial thickening. These changes may however progress to an alveolar inflammation thereby simulating a lobar pneumonia.

Parapneumonic fluid collections may accompany pneumonias. These are usually well seen on radiographs, though occasionally they may be difficult to separate from a consolidation. In such situations, a sonography or CT examination accurately picks up fluid within the pleural space, and enables the interventional radiologist to perform a guided aspiration of the fluid. Examination of the fluid confirms the diagnosis of empyema. Mediastinal adenopathy is not usually present with bacterial pneumonias, but may be seen with tuberculosis, fungal and viral pneumonias. Pneumonia may be complicated by the formation of lung abscess or empyema. The diagnostic feature of a lung abscess is the presence of an air-fluid level. For this to be demonstrated, the patient has to be in the erect position. Occasionally, the abscess may have no significant fluid level and appears as a cavitatory lesion. This needs to be differentiated from a bulla, pneumatocele, or a cavitatory neoplasm. Bullae and pneumatoceles have thin walls whereas lung abscesses have relatively thick walls. A cavitatory neoplasm usually does not have any perilesional inflammation, as is usually seen with a lung abscess. It has been reported that lung abscesses may not be detected radiologically in 18% of cases.[11] A CT scan in these patients becomes mandatory. CT scan clearly demonstrates the air-fluid level in an abscess. CT is also very useful in differentiating between pleural and parenchymal components, which may be superimposed on a plain X-ray, and thus be difficult to differentiate.

ATELECTASIS

Atelectasis is one of the commonest findings on chest X-ray taken in the ICU. The left lower lobe is the most frequent location of atelectasis, especially in the post-bypass patient. The atelectatic portion of the lung has variable radiological appearances. It may be seen as plate-like or linear opacities known as plate atelectasis. Loss of volume is evidenced by shift of the fissures, hilum, diaphragm, trachea and heart. A bronchogram pattern may be seen within the opacity. This is an important finding because patients with an air bronchogram pattern within an atelectatic segment may not improve with bronchoscopy. If no air bronchogram is seen, the patient is likely to improve with bronchoscopic aspiration.[12, 13]

PULMONARY EMBOLISM

The X-ray findings and spiral CT angiography (CTA) scan abnormalities seen in critically ill patients with pulmonary embolism, have been discussed in the Chapter Pulmonary Embolism.

Pleural Effusions

Free pleural effusions tend to gravitate to the most dependent portions of the pleural cavity. On erect chest X-rays, these are seen as homogenous densities in the lower zone with a typical concave or upward-sloping contour, the lateral margin being higher than the medial margin. The posterior costophrenic (CP) sulcus is the deepest portion of the pleura. This is the site where the fluid first tends to accumulate. Radiologically, this is seen as blunting of the costophrenic angle on the lateral view.

At least 200 mL of fluid is required to cause obliteration of the CP angle on a posteroanterior view of the chest, though in some cases, there is no blunting of the angle even when 500 mL of fluid is present. The lateral decubitus view is the most sensitive X-ray to demonstrate free fluid. Fluid is seen layering in the dependent part of the chest wall as a thin uniform opacity. This view however may be technically difficult to obtain in a patient who is critically ill. In patients who are too critically ill to sit erect, a diagnosis of pleural effusion has to be made on a supine X-ray chest. The findings in moderate sized or large effusions are a homogenous opacity of the affected hemithorax with absence of the vascular markings. This is because the fluid is layering posteriorly along the chest wall. Fluid also tends to accumulate along the apex, like an apical pleural cap, and in the base, as these are the most dependent areas on a supine film. Small pleural effusions can be easily missed on a supine radiograph. In fact, only 67% sensitivity and 70% specificity have been reported for the detection of a pleural effusion on supine chest X-ray as opposed to a lateral decubitus view.[14]

In critically ill patients who cannot be positioned for a lateral decubitus view, or if a supine radiograph shows equivocal or negative findings, sonography is an excellent means for demonstrating pleural fluid. This imaging modality is portable and can be easily performed at the bedside. Pleural fluid is seen as an anechoic area separating the echogenic line of the diaphragm and the echogenic inferior margin of the lung. Sonography is also useful in differentiating a pleural effusion from atelectasis/consolidation, which may simulate an effusion on the chest X-ray. Further, it is an excellent guide for thoracocentesis markedly reducing the incidence of iatrogenic pneumothorax.

Occasionally, free pleural fluid may accumulate in a subpulmonic location between the lung and diaphragm, with the lung floating on the fluid. The upper margin of the fluid may then take the appearance of the diaphragm. Left sided subpulmonic effusions may be detected by noting the wide distance between the stomach air bubble and diaphragm. On the right side, differentiation from an enlarged liver pushing the diaphragm upward may be difficult. In these cases, either a lateral decubitus view or sonography is useful to clinch the diagnosis. A loculated effusion may occur when there are adhesions between the visceral and parietal pleura, as a result of which the fluid does not shift with change of the patient's position. Empyema and hemothorax may appear as loculated effusions.

Computed tomography scan is extremely sensitive in detecting even small pleural fluid collections. With the patient supine, free fluid accumulates posteriorly as a hypodense layer conforming to the contour of the chest wall. The presence of septae in the pleural fluid (denoting a likely exudate) is however brought out by a sonographic study rather than by a CT scan. Acute hemorrhage in the pleural space can be well identified by the hyperdensity of blood. CT is also useful in the assessment of the site, extent and wall thickening of the loculated effusions, and for loculated interlobar effusions. These may simulate a mass lesion on plain X-ray but can easily be differentiated on CT. CT with intravenous contrast medium is very useful in differentiating parenchymal from pleural lesions, especially when a plain radiograph has not helped. CT is also an effective guide for thoracocentesis except when the effusion is small and layering posteriorly in the dependent portion of the chest. In these conditions, sonography is far superior to CT.

EMPYEMA

On a chest radiograph, an empyema is usually seen as a loculated fluid collection. It tends to be lenticular in shape as compared to a lung abscess that is rounded. Further, an empyema usually forms an obtuse angle with the chest wall while a lung abscess forms an acute angle. CT is very useful in the diagnosis and management of empyema. On CT scan, an empyema appears as a well-defined fluid collection with enhancing parietal and visceral pleura. This sign of separation of the pleura is known as the split pleura sign. CT scan is far superior to any other imaging modality in differentiating lung abscess from empyema, though occasionally the differentiation may be difficult. On CT scan, a lung abscess is usually rounded whereas an empyema is lenticular in shape. Also, the lung margin is very sharp in relation to an empyema; whereas in a lung abscess, there is usually peripheral consolidation around the abscess.

Traditionally, empyemas have been treated with insertion of chest tubes. The success rate with chest tube drainage is 35–71%.[15] However, 35% of all patients treated with conventional chest tubes are found to subsequently require either open chest tube drainage or decortication. Several studies estimated the success rate of fluoroscopy, sonography and CT scan in image-guided percutaneous insertion of chest tubes to be between 70% and 90%. Under imaging, the catheter can be placed accurately in the fluid collection. In fact, image-guided percutaneous drainage of empyemas is advocated as the primary method of treating empyemas. Patients, who show inadequate drainage or progressive persistent pleural thickening, may finally require decortication.

PNEUMOTHORAX

This is a relatively common complication seen in the ICU and should be very carefully looked for on every chest radiograph of a critically ill patient, especially following procedures such as thoracocentesis, central venous line insertions, endotracheal intubation, tracheostomy and in patients on positive pressure ventilation. Air in the pleural cavity is seen in the most nondependent portion of the chest. On the erect chest X-ray, it is therefore seen in the apical region. There are numerous radiographic signs to recognize a pneumothorax, the most important being demonstration of the visceral pleura as a thin opaque line. Other signs observed are hypertranslucency between the chest wall and the collapsed lung, this region being devoid of vascular markings.

The degree of atelectasis of the underlying lung is variable and depends upon the size of the pneumothorax. The underlying lung shows a mild increase in density but appears opaque only when total collapse has occurred. The size of the pneumothorax may be measured but is usually depicted as small (<25%), moderate (25–50%) and large (greater than 50%). Routine X-rays obtained in the ICU are usually inspiratory films and in these films, a small pneumothorax may be missed. If there is a high index of suspicion, then an expiratory film should be taken to demonstrate a small pneumothorax. Another important point to bear in mind is that a pneumothorax following a procedure may take up to 4 hours to develop; thus, the ideal X-ray to determine a postprocedure pneumothorax is a delayed (4 hours) expiratory film.

Often patients are critically ill and cannot be radiographed in the upright position. The appearance of a pneumothorax on a supine film is different. As air collects in the most nondependent portion (this being the anteroinferior portion on a supine film), this is seen as a hypertranslucency over the upper quadrant with a deep costophrenic sulcus. If these signs are doubtful a cross-table lateral view is obtained, which clearly shows the collection of air.

Occasionally, tubes and skin folds may mimic a pneumothorax; these can however be differentiated by visualizing lung markings beyond these structures. Also skin folds are usually in pairs, bilateral, do not have a sharp margin like the visceral pleura and often extend outside the thorax.

Two unusual types of pneumothorax need to be considered. The more important one is a tension pneumothorax, which is an absolute emergency and, if untreated, will result in death. A tension pneumothorax occurs when air enters during inspiration but cannot exit during expiration due to a check

valve mechanism. On a chest X-ray, the entire hemithorax is hypertranslucent, the mediastinum is shifted to the opposite side and the ipsilateral lung is compressed. In addition, the diaphragm on the affected side may be deeply inverted. The second unusual type of pneumothorax is when there is collapse or lobar atelectasis. There is diffusion of gas into the pleural space due to volume loss. In this scenario, the pneumothorax is essentially an ex vaco occurrence, and resolves spontaneously as the affected portion of lung is better aerated by suctioning or bronchoscopy.[16]

PNEUMOMEDIASTINUM

This may occur following esophageal rupture, tracheobronchial injuries or alveolar rupture with air tracking into the hilum via the interstitium. Air in the mediastinum is seen as a lucency about the mediastinal structures, bounded laterally by an echogenic line—the mediastinal pleura—which is now visualized as it has air on both sides. Air tracking inferiorly in a pneumomediastinum, permits visualization of the infracardiac surface giving rise to the continuous diaphragm sign. In children, the mediastinal air elevates the thymus and outlines it, producing a triangular opacity along the lateral mediastinal border, known as the spinnaker sail sign.

PULMONARY INTERSTITIAL EMPHYSEMA

Pulmonary interstitial emphysema occurs due to elevated intra-alveolar pressure causing rupture of the alveoli, with consequent leak of air into the interstitium. This air then dissects along the bronchovascular bundle that is the path of least resistance. This may extend to the mediastinum, or peripherally to the visceral pleura, resulting in pneumomediastinum or pneumothorax. It may also track superiorly into the neck as subcutaneous emphysema, or rarely decompress into the retroperitoneum as a pneumoperitoneum.

On X-ray, pulmonary interstitial emphysema is difficult to detect and can be seen only when it is superimposed on an area of air space consolidation. It is then seen as thin streaky and bubbly radiolucencies. In fact, when visualized and compared with previous X-rays, it may falsely suggest an improvement in an air space consolidation, as the density of the consolidation becomes less due to the superimposed radiolucencies. This is one paradoxical situation where the patient clinically deteriorates and yet the radiograph shows an apparent improvement. When there is no air space consolidation and the lung is normally aerated, these radiolucencies are not visualized, as they are contrasted against a dark lung. In these cases, a CT scan is very helpful as it demonstrates the linear and cystic areas of air trapping.

TUBES AND SUPPORTING DEVICES

There are numerous tubes and devices used in the ICU for monitoring and support of the critically ill patient. It is important to monitor the position, possible malpositions and complications of these tubes and devices. Portable chest bedside X-rays usually provide adequate information on these devices/tubes.

Airway Tubes

Endotracheal and tracheostomy tube position should be checked immediately after placement and periodically thereafter to ensure proper positioning, as airway tubes if malpositioned may cause serious complications. These tubes usually have a radiopaque line running along their entire length or may be totally opaque. The correct site for the tip of an endotracheal tube is 5–7 cm above the carina with the head in the neutral position.[17] If the carina is not easily delineated, then it is assumed that the carina is between T5 and T7 and the endotracheal tube should end 5–6 cm above the T4/T5 disc space, i.e. between T2 and T4. Changes in head position can alter the site of the tip of the endotracheal tube seen on the radiograph as the tube is usually fixed to the nose or mouth. The tube shifts approximately by 2 cm in flexion or extension. It is, therefore, important to determine the position of the head on the radiograph first. If the tube is too inferior in position, it may be seen to extend into the main bronchus especially the right main bronchus resulting in a bronchial intubation. This results in overinflation of the intubated lung which is therefore at increased risk of barotrauma and pneumothorax. The opposite lung may show changes of atelectasis and collapse. Conversely, an endotracheal tube not inserted inferior enough may extubate or cause vocal cord damage. To prevent vocal cord damage the tip should be at least 3 cm below the vocal cords. Esophageal intubation may rarely occur. This is detected by visualizing the tube outside the tracheal lumen and the presence of gross overdistension of the stomach. Occasionally, it is difficult to determine if the tube is outside the trachea on the frontal radiograph as the esophagus lies behind the trachea. In these cases, a right posterior oblique view with the patient's head turned to the right allows separation of the esophagus and trachea.

A tracheostomy tube tip is ideally situated between half and two-thirds the distance from the stoma to the carina, and the width of the tube should be approximately two-thirds the tracheal width. Tracheal intubation may result in injury to the trachea and consequent tracheal stenosis. Endotracheal intubation may result in subglottic stenosis or stenosis at the cuff site. Anteroposterior and lateral radiographs of the neck and trachea may demonstrate the site and level of stenosis. CT scan is very useful in the demonstration of subglottic and tracheal stenosis, depicting the level, extent and degree of narrowing. Magnetic resonance imaging (MRI) demonstrates the larynx and trachea well and may also be used to demonstrate the site, extent and degree of narrowing.

Nasogastric Tubes

These tubes usually have small rounded radiopaque balls at their lower end denoting the inferior extent of the tube. The ideal location of the tube is in the duodenum as this prevents

gastroesophageal reflux; it also should be kept in mind that the last 10 cm of the tube has side holes; therefore, at least 10 cm should be below the esophageal hiatus. After introduction of a nasogastric tube a radiograph should be taken to determine its location. Occasionally, tubes may be coiled in the pharynx or esophagus, or worse still, they may be in the tracheobronchial tree, which may by result in pneumonia, lung abscess, pneumothorax or a hydropneumothorax. Inadvertent tracheobronchial insertion of a nasogastric tube may occur in patients with endotracheal intubation especially in those with low pressure, high volume balloons, as these do not prevent passage of a feeding tube into the tracheobronchial tree. If inadvertent placement of the tube has occurred into the tracheobronchial tree as seen on X-ray, then the tube is withdrawn and repositioned. A rare malposition has been a perforation of the nasopharynx and base of the skull with an intracranial placement of the nasogastric tube. Rarely, esophageal perforation may result in pneumomediastinum, mediastinal hematoma or pleural effusion. This may occur with a Sengstaken-Blakemore tube when the gastric balloon is inadvertently inflated in the esophagus.

Thoracotomy Tubes

These tubes are frequently used to evacuate air/fluid from the pleural cavity. This is a clear plastic tube with a radiopaque line along its length, which is interrupted by the proximal-most side hole. When used to drain air, it is ideally placed in the second intercostal space anterosuperiorly and directed to the apex. To drain fluid, it is ideally located in the 6th, 7th or 8th intercostal space in the midaxillary line and directed posteriorly. Ideally, the tubes take a gentle curve within the thorax at the site of penetration of the pleura. The tube may be malpositioned in the lung parenchyma or fissures. Malposition in the lung parenchyma usually leads to the formation of a hematoma, bronchopulmonary fistula or parenchymal laceration. Placement of the tube in a fissure results in poor drainage. The malposition may not be appreciated on a frontal radiograph but is usually well seen on a lateral radiograph, as the tube is seen to turn sharply medially when in a minor fissure, and obliquely when in a major fissure. Occasionally, the tube may be malpositioned within the extrapleural soft tissue resulting in inadequate drainage and subcutaneous emphysema. Rapid decompression of the pleural space by the tube may result in a unilateral re-expansion pulmonary edema. A pulmonary infarct may occur if lung tissue is sucked into the tube. Fibrous adhesions may occur around an indwelling tube, so that when the tube is removed, a track persists and may be confused with a pneumothorax. Fluid may accumulate in this tract and appears as an abscess on a chest X-ray. These tracks usually decrease in size over a few days and then finally disappear.

Central Venous Pressure Catheters

Central venous catheters are commonly used in ICU patients to monitor central venous pressure (CVP) and provide a venous access. These catheters are seen as thin radiopaque tubes extending peripherally from the subclavian, internal jugular or femoral vein into the superior vena cava (SVC). The ideal location of the tip of a CVP tube is in the SVC. This is because the tip should be outside the right atrium and beyond the most proximal venous valves, which are usually situated in the subclavian and internal jugular veins.

The CVP catheter may be malpositioned in the internal jugular, opposite subclavian, azygos, brachiocephalic, axillary, hepatic veins or in the right atrium/ventricle. Rarely, there may be a possibility of intra-arterial introduction of a CVP catheter. This may be seen in a hypoxic/hypotensive patient in whom the arterial blood is non-pulsatile and dark, simulating venous blood. As the SVC is a right-sided structure, visualization of the catheter on the left side or in the midline should raise the possibility of an intra-arterial placement.

The main complication of CVP catheter insertion is a pneumothorax. This may occur immediately, or may be delayed for a few hours or even days after insertion due to the slow accumulation of pleural air.[18,19] Therefore radiographs immediately after placement of CVP catheters may not totally exclude a pneumothorax, and delayed films are required. Hemothorax, perforation of the vessel, mediastinal hemorrhage and ectopic infusion of intravenous fluids may occur resulting in radiographic appearances of fluid accumulation at these sites. Venous air embolism is another uncommon complication, which may be visualized on a chest X-ray as air in the main pulmonary artery, with associated signs of pulmonary embolism. Other complications, which may occur, and which are diagnosed on an X-ray are catheter knotting, catheter fragmentation and the catheter pinch-off syndrome. Catheter knotting and fragmentation are serious complications. To visualize the catheter fragments, both frontal and lateral views are required as some fragments may be overlapped on the frontal view. The catheter pinch-off syndrome occurs due to kinking of the catheter between the clavicle, and the first rib resulting in poor catheter function and increased incidence of catheter fracture. This is seen on the radiograph as a focal narrowing of the catheter at the site of kinking.

Pulmonary Artery Catheter

The pulmonary artery catheter is a thin radiopaque tube with a balloon at its terminal end. When in situ it is seen to pass from either the internal jugular vein or subclavian vein into the SVC, right atrium, right ventricle and into the pulmonary outflow tract. The tip of this catheter should lie beyond the pulmonic valve in the right or left pulmonary artery. The catheter tip however should not be more than 2 cm lateral to the pulmonary hilum on the frontal chest radiograph. When the balloon is inflated to measure pulmonary wedge pressure, it is seen as a rounded radiolucency at the tip of the catheter.

Complications, which may occur due to the catheter, are pulmonary infarction if the catheter is placed too distally

and the balloon inflated, thereby occluding a pulmonary vessel. Intracardiac placement of the catheter can result in arrhythmias or perforation. A rare complication is the formation of a pulmonary artery pseudoaneurysm, which is seen on a chest X-ray as a rounded well-defined opacity in relation to the pulmonary artery. This can be easily confirmed with dynamic CT or MRI.

Intra-Aortic Counterpulsation Balloon

The distal tip of this catheter is visualized as a small radiopaque rectangle. The ideal location for this balloon is at the proximal portion of the descending aorta just distal to the left subclavian artery. If the catheter is advanced too far, it may obstruct the left subclavian artery or carotid artery leading to ischemic changes. An abdominal location of the catheter may occur in extensively atherosclerotic or tortuous aortas, resulting in occlusion of the intra-abdominal vessels and consequent renal/mesenteric ischemia. Rarely, this catheter may cause aortic dissection.

Cardiac Pacemakers

These are used in the treatment of bradyarrhythmias and various degrees of heart block. They are usually implanted by either epicardial placement or transvenous placement, the latter technique being more commonly used. On frontal radiographs, the right ventricular electrode of a pacing catheter should point just to the left of the midline, and on the lateral view the catheter projects anteriorly and inferiorly with the electrode seen behind the sternum.

The electrode may be malpositioned in the right atrium, pulmonary outflow tract, inferior vena cava or coronary sinus. This may occur in 3–14% of cases.[20] Most of the above sites of malposition are well-identified on frontal radiographs. A pacing catheter malpositioned in the coronary sinus is difficult to appreciate on a frontal radiograph. A lateral radiograph, however, shows the catheter directed to the posterior aspect of the heart rather than the anterior.

THORACIC AORTIC ANEURYSM

Spiral CT angiography is the modality of choice in the evaluation of thoracic aortic aneurysms. Spiral CTA demonstrates the exact extent of the aneurysm in multiple planes. Further, the mural thrombus and true lumen are well visualized. Though angiography has been considered the gold standard in evaluation of thoracic aortic aneurysms, it only demonstrates the true lumen of the aneurysm. The mural thrombus and aortic wall are not demonstrated on angiography. Spiral CTA also visualizes the arch vessels and defines the relationship of the arch vessels with the aneurysm, the effect of the aneurysm on adjacent structures, and in case of aortic rupture demonstrates a periaortic hematoma. Spiral CTA provides information regarding lumen/wall/structures outside the wall, rules out other clinical conditions, which may simulate dissection.

AORTIC DISSECTION

Spiral CTA is the ideal technique to evaluate aortic dissection. The definitive diagnosis of aortic dissection requires the identification of the intimal flap, which is seen as a linear density within the lumen of the aorta separating the true and false lumens. In chronic dissection, CTA can also demonstrate thrombosis within the false lumen. MRI also demonstrates whether the aortic branches arise from the true or false lumen, and also identifies the most serious complication of dissection, viz. aortic rupture.

A diagnostic problem, which affects CT, MRI and angiography, is the differentiation between a completely thrombus-filled false channel, and a thoracic aortic aneurysm with a mural thrombus. If the patent lumen is eccentric and appears to be compressed, if the thrombus extends for greater than 7 cm, and if the thrombus changes position within the aorta at different levels, then it is more likely to be related to dissection.

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CHAPTER 11

Imaging Techniques in the Abdomen

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GENERAL CONSIDERATIONS

The radiologist is now well-armed with a full complement of diagnostic modalities to evaluate the abdomen in a critical care setting. These modalities are also an excellent guide for therapeutic procedures. A plain X-ray of the abdomen (erect and supine) is usually the first investigation ordered. These films are very useful in diagnosing perforation, bowel obstruction, bowel ischemia and other bowel pathologies. Calcification, calculi, foreign bodies and information regarding the position and placement of tubes, are easily detected on plain X-rays.

A chest X-ray is also mandatory as this is the best view to demonstrate a pneumoperitoneum with gas under the diaphragm. A number of chest pathologies may present clinically as an acute abdomen, e.g. pneumonia, congestive heart failure, myocardial infarction, dissecting aortic aneurysm, pulmonary infarction and pericarditis. Acute abdominal conditions can also cause respiratory complications, chiefly pleural effusion, atelectasis and aspiration pneumonia. Finally, an X-ray of the chest on admission provides a good baseline study. Postoperative complications like a subphrenic abscess may cause subtle changes on an X-ray, which may be evident only on comparison with a baseline X-ray.

Sonography is indispensable in the evaluation of the abdomen and pelvis in critically ill patients with acute abdominal problems, as it can be performed at the bedside. In fact, it is the modality of choice for evaluation of the gallbladder, free fluid, genitourinary system, and compares well with computed tomography (CT) in evaluation of the liver. Unfortunately, bowel gas, obesity, wound dressings, and abdominal scars interfere with sonographic evaluation.

A CT scan is the modality of choice as it can image the entire abdomen and pelvis, and factors which interfere with sonographic evaluation do not hamper a CT scan. The only disadvantage is the need to transport the patient to the CT scanner suite. However, the information that is gained far outweighs the risk of transportation of the patient.

Spiral CT angiography is an excellent noninvasive modality to visualize the abdominal vasculature especially aortic aneurysms.

Magnetic resonance imaging (MRI) of the abdomen and pelvis has shown significant improvement over the last few years. Unfortunately, it is a lengthy procedure; however, it is useful in vascular pathologies where spiral CT angiography is contraindicated such as when serum creatinine is elevated or there is known allergy to contrast media. Angiography is now mainly used as a combined diagnostic and therapeutic procedure for the treatment of GI hemorrhage.

ACUTE CHOLECYSTITIS

Sonography is the modality of choice in evaluating acute cholecystitis. The hallmark of acute cholecystitis is the presence of gallstones with a positive sonographic Murphy's sign. These features are present in 92% of cases of acute cholecystitis.[1] The sonographic Murphy's sign is similar to the clinical Murphy's sign. The only difference being that pressure is applied by the sonography transducer instead of the clinician's hand. This sign is more sensitive than the clinical sign as the transducer is applied exactly over the site of the gallbladder. Gallstones are seen as echogenic (bright) dependent shadows, which are accompanied by acoustic shadowing below the calculi due to the reflection of the sound waves by the calculi. The calculi are usually mobile and move

with change in the patient's position; occasionally they may be impacted at the neck of the gallbladder and in these situations do not move with change of position. Other sonographic findings are gallbladder wall thickening, presence of sludge and pericholecystic fluid. These signs are not specific as they are seen in a variety of other conditions. The gallbladder wall is considered to be thickened when it exceeds 3 mm in diameter. Sludge in the gallbladder may be seen as echogenic material layering the dependent portion of the gallbladder with no shadowing. Pericholecystic fluid is seen as a thin halo around the gallbladder.

Complications of acute cholecystitis are gangrenous cholecystitis, emphysematous cholecystitis and perforation. Gangrenous changes are reported to occur in 2–38% of cases of acute cholecystitis.[2] On sonography, this appears as marked asymmetry of the gallbladder wall evidenced by focal wall thickening and irregularity of the wall. These changes are due to mucosal edema, necrosis, ulcers, intramural hemorrhage and microabscesses in the gallbladder wall. There may also be intraluminal echoes due to sloughing of the gallbladder mucosa and fibrous or mucosal debris. An important sonographic sign in gangrenous cholecystitis is the conversion of a positive sonographic Murphy's sign to a negative sonographic Murphy's sign due to denervation of the gallbladder. This is usually accompanied by diffuse abdominal pain. Emphysematous cholecystitis is a severe variant of acute cholecystitis, which occurs due to gas-forming bacteria invading and devitalizing the gallbladder wall. More than one-third of patients with emphysematous cholecystitis are diabetics; gangrene and perforation of the gallbladder are important complications. The sonographic findings depend upon the demonstration of gas which is released by the bacteria into the lumen or the wall of the gallbladder. Air in the lumen is seen as an echogenic (bright) nondependent area, whereas air in the gallbladder wall is seen as a curvilinear or arc-like echogenic area.

Perforations occur in 5–10% of cases with acute cholecystitis.[3] It can present in three forms: (1) an acute form which results in generalized peritonitis; (2) a subacute form which results in the formation of a pericholecystic abscess and (3) a chronic form which results in an internal biliary fistula. Most cases are of the subacute variety resulting in abscess formation at the fundus of the gallbladder. It is important to differentiate an intraperitoneal abscess from a gallbladder bed or intramural abscess, as the former requires surgery and the latter can be managed conservatively. Abscesses are seen as ill-defined hypoechoic to echogenic collections in relation to the gallbladder. CT is considered superior to sonography in the evaluation of gangrenous changes as well as pericholecystic abscesses. Gangrenous changes are demonstrated on CT as an irregularity of the inner gallbladder surface due to sloughing of the mucosa or as frank disruptions in the continuity of the gallbladder wall. Pericholecystic abscesses are seen as contrast-enhanced CT reveals a thick-walled irregular enhancing lesion with a necrotic core, adjacent to the gallbladder. MRI demonstrates similar features.

ACALCULOUS CHOLECYSTITIS

In 5–10% of cases of acute cholecystitis, no calculi can be demonstrated in the gallbladder.[4] This form of cholecystitis has a higher mortality and morbidity rate, and is seen particularly in patients following trauma, surgery, sepsis, and burns; it is also observed in critically ill patients with shock and poor perfusion, in patients with diabetes mellitus, and in hyperalimentation. Gangrene and perforation are common complications. The sonographic signs are limited by the absence of calculi and diagnosis rests on demonstration of the sonographic Murphy's sign, gallbladder wall thickening, presence of sludge and pericholecystic fluid. When there is a high index of suspicion on clinical grounds but imaging findings are negative, an imaging-guided aspiration of the gallbladder contents may be performed and the fluid sent for bacteriology and leukocyte count. In patients who are too ill to undergo surgery, a percutaneous cholecystostomy may be performed by the introduction of a catheter into the gallbladder under imaging guidance. Using sonography a 97.5% success rate has been reported for cannulating the gallbladder.[5] Complications that may occur with this procedure are biliary peritonitis, bilioma, hemobilia, and vagal reaction. However, the reported complication rate in elderly patients is 10% which is far better than the surgical complication rate for cholecystectomy which is 24%.[5] Therefore, in a critically ill patient, percutaneous cholecystostomy can be used as a temporizing procedure till such time as the patient is ready for cholecystectomy.

PANCREATITIS

Computed tomography is the imaging modality of choice for evaluation of acute pancreatitis. It is not limited by gaseous shadows in the intestinal loops, by abdominal bandages, or by an obese abdominal wall; it also evaluates the retroperitoneum extremely well.

Sonography has limited use in the evaluation of acute pancreatitis. It is useful for detecting biliary calculi as a cause of pancreatitis and helps in the follow-up of pancreatic fluid collections. It is also useful as a guide for aspiration of fluid collections. The inflamed pancreas may be visualized on sonography as an enlarged gland with a decrease in its echogenicity due to edema of the gland. However, as necrotic areas are not evaluated well by sonography, CT becomes mandatory.

Magnetic resonance cholangiopancreatography (MRCP) is particularly useful in the evaluation of the etiological cause of acute pancreatitis. It has a sensitivity of close to 100% in detecting calculi as small as 2 mm. It is also useful to detect pancreas divisum.

There are two distinct forms of pancreatitis: (1) acute edematous pancreatitis and (2) acute necrotizing pancreatitis. In acute edematous pancreatitis, there is only mild swelling of the pancreas with loss of normal lobulations and a diffuse decrease in attenuation of the pancreas. This form of

pancreatitis runs a mild course and rarely progresses to acute necrotizing pancreatitis with its associated complications.

Acute necrotizing pancreatitis is a fulminant form of pancreatitis in which there is necrosis of the pancreas. These areas of necrosis may be diffuse or focal, consisting of nonviable pancreatic parenchyma which varies in size, location and extent. A dynamic contrast-enhanced CT accurately defines the extent of pancreatic necrosis; this has been found to correlate very well with the extent of necrosis found at surgery. Necrosis is seen on CT as areas within the pancreas which exhibit no enhancement. These necrotic areas have a very important bearing on the course of pancreatitis, as they are liable to undergo secondary infection and form pancreatic abscesses. The more extensive the pancreatic necrosis the greater is the morbidity and mortality. Patients with no pancreatic necrosis have been found to have a 0% mortality and a 6% complication rate, whereas patients with pancreatic necrosis have a 23% mortality rate and a 82% complication rate.[6]

Patients with acute necrotizing pancreatitis usually have accompanying peripancreatic changes in the form of edema, effusions and peripancreatic necrosis. Edematous changes in the peripancreatic region are manifested by a subtle increase in the density of the peripancreatic fat, which on CT has a nonhomogenous appearance with strands and thickened fascial planes. The anterior pararenal fascia is often thickened; this is more evident on the left than on the right side. Effusions or acute fluid collections are enzyme rich pancreatic juice collections seen in about 40% of patients with acute pancreatitis.[7] The fluid collections usually develop around the inflamed gland; they are localized only by the anatomical space in which they collect. Peripancreatic fluid collections are very well-demonstrated by CT scans, and are most commonly seen in the anterior pancreatic region, the lesser sac, the anterior pararenal, perirenal, posterior pararenal regions, and rarely in the mesocolon and the root of the mesentery. These fluid collections are usually limited by the thickened pararenal or Gerota's fascia. The quantity of fluid in these effusions is variable and can range from a small amount to large quantities. Of these collections, 50% resolve spontaneously; the remainder may evolve into pseudocysts.[8]

Sepsis

Sepsis is a major complication of pancreatitis and is accompanied by a high incidence of mortality and a prolonged hospital stay. Pancreatic abscesses occur following secondary infection of parenchymal pancreatic necrosis, peripancreatic necrosis, effusions and pseudocysts. Detection of the development of sepsis in these areas is very difficult even with a CT, the only sure sign being the presence of gas due to secondary infection by coliform bacteria. Gas is seen in the fluid collection as very dark well-defined bubbles. Occasionally, gas may be present due to a gastrointestinal (GI) fistula or previous surgery. It is important to note that a small amount of fat may be seen interspersed with a peripancreatic necrosis as a result of fat necrosis; this should not be confused with air bubbles, which are indicative of abscess formation. The differentiation is easy by CT, the values of fat ranging between –20 Hu and –80 Hu, and of air being more than or equal to –300 Hu. Also air bubbles have well-defined margins and are homogeneously jet black, whereas fat is non-homogeneously gray with ill-defined margins.

Since the presence of air is seen only in a small percent of patients with pancreatic abscesses, the diagnosis of pancreatic sepsis has to be made by CT-guided aspiration. All sites of fluid collection, parenchymal necrosis and peripancreatic phlegmon are subjected to CT-guided aspiration. This is a tedious process and requires a dedicated interventional radiologist as there are often more than 5–6 sites from, which it may be necessary to obtain samples. The sites of aspiration are marked and guided by CT, a fresh needle and syringe being used for each site. Care is taken not to go through the large bowel as the colon has a large number of bacteria, and transgressing it could result in colonic bacteria contaminating the CT-guided aspiration sample, with false positive results. Further, colonic bacteria may be inoculated into the effusion or acute pancreatic fluid collection thereby converting a sterile collection into an infected one. Technical expertise is therefore of utmost importance. Complications of the procedure include pnuemothorax or empyema if the pleura is transgressed, hemorrhage due to trauma to a vessel, and secondary infection.

It is crucial from the management point of view, to differentiate an abscess from infected necrosis. An abscess may be treated by percutaneous drainage, whereas infected necrosis developing in relatively solid tissue can be treated by surgical debridement alone. On CT an abscess is seen as a peripancreatic fluid collection, which is composed of liquid pus, as determined by needle aspiration. Infected necrosis is seen on CT as a non-enhancing solid or partly liquefied soft tissue, which reveals infected material on needle aspiration. As the CT appearances of an abscess and infected necrosis may be similar, needle aspiration is crucial in differentiating between the two conditions.

Pancreatic sepsis is treated by surgical debridement, necrosectomy and drainage through thick tubes. CT is invaluable in surgical planning and in the follow-up of postoperative patients to evaluate any fresh collection and to determine whether the drains are well sited or not. Patients who are too critically ill to undergo surgery for pancreatic sepsis, may benefit from CT-guided introduction of pigtail and surgical drainage tubes. These CT-guided procedures are extremely successful elsewhere in the abdomen; however, in pancreatitis they have met with only limited success. This is due to the fact that the sepsis of pancreatic necrosis and peripancreatic necrosis usually causes infection in solid tissues which requires manual debridement, and attempts to drain this prove futile. Interventional radiology is mainly a temporizing procedure, which helps to tide the patient over a period of time, till the patient is deemed fit for surgery.

PSEUDOCYSTS

Pseudocysts are round or oval encapsulated fluid collections containing necrotic material, proteinaceous debris and enzymatic material. On CT, a pseudocyst appears as a well-defined fluid collection with a thin capsule. The most common location for pseudocysts is the lesser sac, although they may be found anywhere in the mediastinum, abdomen or pelvis as they may dissect along fascial planes, along vessels and through capsules of solid organs. Complicated, enlarging or symptomatic pseudocysts require percutaneous catheter or surgical drainage.

Infected pseudocysts are treated by percutaneous drainage. The management of a noninfected pseudocyst is controversial. Surgical treatment is only undertaken when the wall is mature after several weeks. Large pseudocysts greater than 5 cm in size can easily be drained percutaneously. The cure rates are reported to be 85% with percutaneous drainage, the drainage period averaging about 20 days.[9]

RETROPERITONEAL HEMORRHAGE

Retroperitoneal hemorrhage may occur as a late complication due to vascular injuries produced by the extravasated pancreatic enzymes. These injuries result in the formation of a pseudoaneurysm which may rupture resulting in massive hemorrhage. This is seen on CT as high density fluid in the retroperitoneum, or as a pseudocyst. The commonly involved vessels are the splenic or pancreaticoduodenal arcade. The diagnosis is usually confirmed by angiography and subsequently treated by embolization of the bleeding vessel.

Grading

Computed tomography may be used as a prognostic indicator of the severity of acute pancreatitis. The patients are classified into five grades—

1. Grade A: Normal CT of pancreas.
2. Grade B: Diffuse pancreatic enlargement with or without parenchymal necrosis.
3. Grade C: Pancreatic enlargement with necrosis and peripancreatic edema.
4. Grade D: Pancreatic involvement with a single ill-defined peripancreatic fluid collection or phlegmon.
5. Grade E: Two or more fluid collections and/or the presence of gas.

Most complications of acute pancreatitis occur in Grade D and E patients. A more accurate grading system is the CT Severity Index (CTSI), in which patients are assigned 0–4 points depending upon their grade (from A to E). To this 2, 4 or 6 points are added depending upon the extent of pancreatic necrosis—30% necrosis or less is given 2 points; 30–50% necrosis is given 4 points, and more than 50% necrosis is given 6 points. Thus, the patients are graded on a scale of 0–10. Those with a score of 0–1 showed no mortality or morbidity. Patients with a score of 2 had no mortality and only a 4% morbidity. Patients with a score between 7 and 10 had a 17% mortality and a 92% complication rate.[8]

It is often confusing to the clinician when to order a CT scan in acute pancreatitis. It has been suggested that an initial CT study should be done: (1) in patients in whom the diagnosis is in doubt; (2) in patients with severe pancreatitis accompanied by fever, tenderness and leukocytosis; (3) in patients who do not improve within 72 hours of conservative treatment; (4) in patients with a Ranson score more than 3 or an acute physiology and chronic health evaluation II (APACHE II) score more than 8; (5) in patients who show initial good improvement, but then rapidly deteriorate. A follow-up CT study is done: (1) in patients with CT scan Grade A to C, or CTSI of 0–2, only if there is a clinical suspicion of a complication; (2) in patients with a CT scan Grade D or E, and CTSI of 3–10 after 7–10 days. Further, CT scans of patients with Grade D/E, and CTSI 3–10, are performed only if the clinical status deteriorates or does not improve. A final CT is done in this group of patients at the time of discharge as important complications may develop without clinical symptoms. It must be remembered that the resolution of the CT features of pancreatic or peripancreatic inflammation lag behind clinical improvement.

Appendicitis

This is the most common surgical emergency with a lifetime risk of 6.7% in women and 8.6% in men.[10] A careful history and thorough physical examination are adequate in most cases to make a diagnosis, imaging having no role to play in these cases. However, approximately 20% of cases have an atypical presentation, especially in elderly patients where there may be minimal pain, in children where an accurate history is not available, and in ovulating women who have a misdiagnosis rate of about 40%, due to pathology in the ovaries, Fallopian tubes, uterus or bladder.[11] In these cases, imaging is useful to clinch the diagnosis, or exclude other conditions, which may be mistaken for appendicitis.

The plain film seldom provides much help in the diagnosis; the presence of a distended cecum with an air or fluid level, or terminal ileal ileus is nonspecific and unreliable signs. Appendicoliths are specific findings on a plain film that generally confirm a diagnosis of appendicitis. These are seen as round or oval opacities, 0.5–2 cm in diameter, with a calcified laminated rim. In 10% of cases of acute appendicitis an appendicolith may be seen; however, 50% of these cases are usually associated with perforation.[11] Over the past 5 years improvements in US/CT technology, techniques and interpretations have substantially improved the sensitivity, specificity and accuracy of ultrasound (US) or CT in diagnosing acute appendicitis. Graded compression sonography has shown a sensitivity of 77–89% and a specificity and accuracy in 90%of cases of acute appendicitis.[11-14]

A high resolution (5–7.5 Hz) transducer is placed over the area of maximal tenderness and pressure is applied slowly and gently to minimize pain and discomfort. This procedure

of graded compression sonography displaces bowel loops and gas, reducing the distance between the transducer and the appendix and thereby providing better resolution, as well as information regarding compressibility of the appendix. On sonography an inflamed appendix is seen as a tubular fluid-filled structure more than 6 mm in diameter, devoid of peristalsis and noncompressible.

Computed tomography is superior to sonography with a 98% sensitivity, 83% specificity and 93% accuracy as it directly visualizes the appendix, the pericecal region and other intra-abdominal structures.[15] Sonography is not able to image well in the obese patient and in those with significant tenderness preventing adequate compression. On CT, the inflamed appendix is seen as a tubular fluid-filled structure approximately 0.5–2 cm in diameter with a thickened enhancing wall which is usually 3 mm or more in diameter. Pericecal inflammatory changes may be seen in the form of pericecal fascial thickening, altered density of pericecal fat, ill-defined phlegmonous soft tissue, and occasionally a fluid containing area representing an abscess. The presence of pericecal inflammatory changes alone, without visualization of the inflamed appendix is not diagnostic but makes the diagnosis highly probable. Adnexal cysts, masses, salpingitis, tubo-ovarian abscess, ureteric calculi, lymphadenitis and ileitis may clinically mimic appendicitis, but ultrasonography or CT helps to differentiate between these conditions.

In women of childbearing age an ectopic pregnancy or a ruptured ectopic pregnancy must be kept in mind as a differential diagnosis. Sonography is the modality of choice in evaluating an ectopic pregnancy, and is preferably done by both the transabdominal and transvaginal routes. The surest sign of an ectopic is the presence of an extrauterine gestational sac; this is seen in only 20% of cases. The other important sign is the extrauterine sac sign seen in 70% of cases.[16] A ruptured ectopic is seen as an adnexal hematoma; on the US, this appears as a complex hyperechoic adnexal lesion often accompanied by echogenic free fluid.

Pneumoperitoneum

Demonstration of a pneumoperitoneum is one of the most important signs in medicine, as it generally warrants emergency surgery. The best view to demonstrate a pneumoperitoneum is the erect frontal chest X-ray, which demonstrates gas under the domes of the diaphragm better than an erect abdominal X-ray. This is because the exposure factors used are higher in abdominal X-rays and the X-ray beam is tangential to the diaphragm, resulting in a darker appearance of the diaphragmatic region with consequent difficulty in demonstrating gas under the diaphragm. In nearly 75–80% of perforations of a hollow viscus, free air is demonstrated on a radiograph and 75% of these cases are visible on a frontal chest X-ray. In a small percentage of patients (10%), when the frontal chest radiograph fails to demonstrate free air, a left lateral decubitus view may be used. This view is very useful to demonstrate small quantities of free air. The patient is positioned on his side with the left side down and the right side up. At least 10 minutes must elapse to permit the free air to migrate to a nondependent position, i.e. between the right margin of the liver and the lateral abdominal wall, and a horizontal radiograph is taken with the X-ray cassette behind the patient. Free air is seen as a crescent between the liver and right abdominal wall. This position is difficult as it may be cumbersome for the patient to lie in this position for 10 minutes, and at least 2–3 attendants are needed to position the patient for this view. Therefore, in patients who are critically ill, traumatized or comatose, erect and left lateral decubitus views may be technically difficult. In such patients, only a supine radiograph of the abdomen is possible. However, this view is not very useful and a pneumoperitoneum can be easily missed.

Postoperative pneumoperitoneum may be seen for a few days (generally about 3 days), after which time, the free air is resorbed. Occasionally, free air may be seen for up to 24 days. The resorption rate is said to be much greater in obese individuals than in thin individuals. It is important to detect a fresh postoperative leak of air which is diagnosed by an increase in the amount of air, or with the help of contrast studies or CT scan.

INTESTINAL OBSTRUCTION

Mechanical obstruction of the bowel is produced by occlusion or constriction of the lumen; this may progress to strangulation, interruption of blood supply with subsequent mucosal ulceration, bowel necrosis and perforation. Obstruction may occur in the small or large bowel.

Small Bowel Obstruction

The most common cause of small bowel obstruction is adhesions (occurring in 75% of cases). In fact, 5–20% of patients who have undergone abdominal surgery will develop small bowel obstruction. On an erect abdominal X-ray, dilated small bowel loops with multiple air fluid levels are visualized. Usually, the dilated loops are in the form of an inverted U with fluid levels in both limbs. Occasionally, in a nonobstructed patient, a few air-fluid levels may be seen, but if more than 3 levels are seen, or if they are present in the left hypochondrium, there is a strong possibility of obstruction. When there is a high jejunal obstruction dilated loops may show a typical appearance known as the string of pearls sign. In this sign, the obstructed bowel loops are fluid-filled and small bubbles of air collect on the surface giving rise to the string of pearls sign.

The site of obstruction in the small bowel, whether jejunal or ileal can be differentiated by noting the pattern of the dilated bowel loops. Jejunal loops have a typical appearance in the form of concentric bands extending across the lumen, known as valvule conniventes. Ileal loops have a featureless appearance, appearing like a tube. A barium enema may be used to differentiate a colonic from a distal small bowel obstruction.

Computed tomography is very useful in the evaluation of a small bowel obstruction and has a sensitivity of 94% and specificity of 96%.[17-19] A small bowel diameter of more than 3 cm indicates that the bowel is dilated. CT also demonstrates a transition zone between the dilated proximal loops and the decompressed distal bowel, this sign is diagnostic of small bowel obstruction. As CT is also able to demonstrate the peritoneal surface of the bowel, tumor or inflammatory mass lesions can thereby be detected or excluded. Absence of tumor or inflammatory processes suggests that the cause of obstruction is an adhesion.

A rare form of small bowel obstruction is gallstone ileus. This occurs due to erosion of a gallstone into the duodenum, the gallstone lodging in the ileum and causing ileal obstruction. The radiological features are the presence of a gallstone in the lower abdomen, dilated small bowel loops and air in the biliary tree.

A diagnosis of intussusception can also be made on CT which shows a typical appearance. As the intussusceptum enters the intussuscipiens, there is trapping of the fatty mesentery and a complex composed of the intussusceptum and the intussuscipiens is seen on CT as concentric cylinders with fat density interposed between them.

Large Bowel Obstruction

The most common cause of large bowel obstruction is carcinoma, about 60% of growths being situated in the sigmoid colon. Other causes are diverticular disease and volvulus of the colon. The radiographic signs of large bowel obstruction depend upon the state of the iliocecal valve. If the iliocecal valve is competent (Type I), there is gross distension of the cecum and the large bowel. If the ileocecal valve is incompetent (Type II), there is no distension of the large bowel, and the appearance is that of a small bowel obstruction. The cecum may perforate in a Type I obstruction. A distended colon is evidenced by the presence of its haustral markings which are seen as asymmetric folds. This is an important distinguishing feature from small bowel obstruction.

Paralytic Ileus

Paralytic ileus occurs commonly following surgery, especially where excessive bowel manipulation has been performed, and in peritonitis. Fluid and gas accumulate in the dilated small and large bowel loops as a result of cessation of intestinal peristalsis. On plain radiographs, these features are seen as dilated small and large bowel loops with multiple air-fluid levels. In view of the dilated large bowel loops, it is difficult to differentiate a distal large bowel obstruction from a paralytic ileus. The differentiation is possible if air is demonstrated in the rectum or distal large bowel. If this is not demonstrated on a plain film then a right lateral decubitus and/or prone film may be taken. In the right lateral decubitus view, air rises into the distal colon and in a prone film air migrates into the rectum. If these are not conclusive then a contrast enema may be required to exclude distal obstruction. Alternatively, a CT can be performed to demonstrate air in the rectum or sigmoid; this excludes an obstruction. If there is suspicion of a perforation or if the colonic diameter exceeds 5.5 cm, a water-soluble contrast should be used instead of barium.

Localized ileus is seen adjacent to the site of inflammation, e.g. cholecystitis, pancreatitis, appendicitis, and is visualized as isolated dilated small bowel loops with a few fluid levels. Ogilvie's syndrome is a condition seen in elderly debilitated patients who have a major underlying systemic abnormality such as severe infection, recent surgery or cardiac disease. There is marked dilatation of the colon and occasionally there is associated with small bowel ileus. This condition is also known as pseudo-obstruction. In view of the markedly distended large bowel, these patients are prone to cecal perforation, especially when the cecum is dilated to more than 9 cm for 2–3 days. Colonic and cecal distension can be treated by colonoscopic decompression.

Toxic Megacolon

Toxic megacolon is a fulminant form of colitis in which there is marked dilatation of the colon (diameter >5.5 cm). The radiographic features are most commonly seen in the transverse colon as this is the region where gas accumulates in the supine posture. In addition to marked distension of the colon, there is thickening of the wall or mucosa with numerous nodular areas projecting into the bowel lumen representing mucosal islands (spared mucosa), adjacent to the areas of ulceration. The haustra are effaced and a thumb-printing pattern may be seen. A contrast enema is contraindicated due to the high risk of perforation, but a CT may be useful in demonstrating the wall thickening.

Ischemic Colitis

Ischemic colitis may be caused by primary ischemia due to mesenteric arterial stenosis, thrombosis or venous occlusion. Occasionally, strangulation or obstruction of the bowel may lead to ischemic changes. Any part of the small bowel may be involved, but in the colon, it is usually localized to the distal colon supplied by the inferior mesenteric artery. Segmental ischemia may result in strictures and occasionally transmural infarction may progress to perforation. On radiographs, the characteristic signs are edematous thickened loops with a thumb-printing pattern due to submucosal hemorrhages. There may be air in the bowel loop wall (pneumatosis intestinalis), and air in the portal venous system. Other non-specific findings are small bowel ileus, or an X-ray plate which remains dark through lack of gas within the small gut.

Computed tomography is very useful in the evaluation of ischemic bowel; it may demonstrate the direct signs of mesenteric arterial or venous thrombosis and secondary signs of thickened bowel loop walls, pneumatosis intestinalis and portal venous air. Ascites and bowel distension may also be seen. A nondiagnostic CT or plain film does not exclude ischemic colitis and if there is a strong clinical suspicion, angiography should be performed. Angiography may be both

diagnostic and therapeutic; vasodilators and thrombolytic therapy may be used as therapeutic interventions.

GASTROINTESTINAL HEMORRHAGE

Angiography has a useful role to play in detecting the cause, and the subsequent management of upper and lower GI bleeds. The cause of upper GI bleeds is usually evident on an upper GI endoscopy; if this fails, then angiography is used to determine the site of bleeding. The limitation of angiography is that the rate of blood loss should be at least 5 mL/minute, or if superselective catheters are used at least 1 mL/minute, to be able to detect the site of bleeding. The site of bleeding is identified on angiography as a diffuse blush of extravasating contrast. Once the site is localized vasopressin may be injected through the catheter at the rate of 0.2 units/minute, to help control the bleeding. The duration of the therapy is 20–40 minutes. Occasionally, it may be longer in elderly atherosclerotic individuals.

Epinephrine may also be used in a dosage of 8–30 μg/minute. Infusions into the left gastric artery usually control bleeding from Mallory-Weiss tears, gastritis, and stress ulcers of the upper part of the stomach. An infusion into the common hepatic artery is useful for antral lesions, and gastroduodenal arterial infusions usually control duodenal bleeding.

An infusion of vasopressin into the superior mesenteric artery may be used to control bleeding due to portal hypertension by lowering the venous pressure. Complications of vasopressin therapy are water retention, abdominal cramps, diarrhea, and occasionally cardiotoxicity. Vasopressin effectively controls bleeding from small vessels and capillaries as seen in mucosal tears and stress ulcers. However, bleeding from large arteries, as in duodenal ulcer, may not be controlled and may require embolization of the vessel.

Different materials have been used for embolization—coils, glue, gelatin or fiber, each having its own advantages and disadvantages. Coils and glues are most commonly used. These are injected through the catheter at the site of bleeding in an attempt to occlude the bleeding vessel. As bleeding from large arteries is not effectively controlled by vasopressin, embolization is advocated as the primary procedure. Lower GI bleeds usually occur as a result of bleeding from colonic diverticulitis. These usually respond well to vasopressin therapy.

ABDOMINAL AORTIC ANEURYSMS

Abdominal aortic aneurysms are usually infrarenal in location and may be fusiform or saccular. Sonography usually detects nearly all abdominal aortic aneurysms; however, CT is required for further evaluation to determine the extent of the aneurysm. On CT, abdominal aortic aneurysms are usually more than 3 cm in diameter with calcification of their walls. There is usually an associated mural thrombus, which is seen as a circumferential thrombus along the wall of the aorta. Occasionally, it may be eccentric along the anterolateral wall, and may be difficult to differentiate from a chronic dissection.

Computed tomography is very useful in determining the extent of the aneurysm—whether it is infrarenal, or involves the renal or superior mesenteric arteries, or if there is any inferior extension into the iliac vessels. These points are very important in planning surgical intervention. MRI is a useful modality for evaluating the aorta, its main advantage being its ability to image in multiple planes; also there is no need to inject intravenous contrast medium as flowing blood is seen as a signal void. Angiography has been the age-old modality for evaluating abdominal aortic aneurysms, but with the current imaging modalities available, it is no longer necessary. In fact, angiography is limited to defining only the patent lumen of an aneurysm, as the extraluminal thrombosed component, which is well visualized on US/CT/MRI, is not demonstrated on angiography.

ABDOMINAL AORTIC DISSECTION

Aortic dissection is fortunately a rare complication of aortic aneurysms, and usually occurs as an inferior extension of a dissecting thoracic aneurysm. The CT, MRI, and angiographic imaging characteristics are similar to those of dissecting aneurysms of the thoracic aorta, and have been discussed earlier.

ABDOMINAL AORTIC RUPTURE

This is a catastrophic event requiring emergency surgery. The crux of the diagnosis lies in the demonstration of a retroperitoneal hematoma adjacent to an abdominal aortic aneurysm. In this emergency situation in a critically ill patient with rapidly dropping blood pressure, sonography is invaluable as it is portable and can be performed at the bedside. A retroperitoneal hematoma is seen as an ill-defined mixed echoic lesion adjacent to the aorta. However, sonographic examination is often hampered by bowel gas especially if the patient is obese. CT is an ideal investigative modality and will demonstrate a mildly hyperdense collection in the pararenal regions adjacent to the aorta. Occasionally, a discontinuity of the aortic wall may be seen on CT. MRI similarly is useful in the detection of a retroperitoneal hematoma which is seen as a mixed intensity retroperitoneal lesion. T1-weighted images are only required to detect the hematoma, a breach in the aortic wall may also be seen on MRI. MRI has a disadvantage of being a much longer procedure with difficulty in monitoring the patient, and therefore CT is the modality of choice.

RENAL INFLAMMATORY PROCESSES

Acute pyelonephritis usually follows infection in the bladder which ascends to involve the renal pelvis and renal parenchyma secondarily. Sonography is usually negative although occasionally may demonstrate an enlarged hypoechoic kidney. CT is more sensitive and specific. The affected kidney

is seen to be enlarged; following administration of intravenous contrast medium the nephrogram has a striated and blotchy appearance due to areas of decreased enhancement or non-enhancement, which subsequently on delayed scans show filling in of contrast. In acute bacterial nephritis, the changes are similar but are more marked. Occasionally, the changes seen on CT may be more lobar extending to the hilum.

Acute lobar nephroma (preabscess) usually occurs due to a partially treated infection and appears as a focal area of inflammation with small necrotic areas. On sonography, these changes may appear as a mass like hypoechoic lesion mimicking a neoplasm. On CT, they appear as a hypodense lesion with small necrotic areas within it, of near water density. These may resemble renal infarct or ischemic areas.

Sonography is usually effective in the detection and evaluation of renal abscesses, which are greater than 2 cm in size. They appear as relatively well-defined hypoechoic or mixed echoic lesions, which may be uniloculated or multiloculated. The presence of debris is very suggestive of an abscess. CT has a much better sensitivity and specificity for renal abscesses as it also depicts the perinephric and retroperitoneal inflammatory changes. On CT, these appear well-defined hypodense collections, which may have debris in the form of a fluid level. Perinephric changes may be present in the form of fascial thickening or perinephric or psoas extension of the abscess.

Pyonephrosis occurs when there is infection of an obstructed collecting system. Sonography is an excellent modality for evaluating pyonephrosis and shows evidence of debris layering in the dilated pelvicalyceal system. Sonography can also be used as a guide for aspiration as well as percutaneous nephrostomy.

EMPHYSEMATOUS PYELONEPHRITIS

This is the most severe necrotizing renal infection and mainly occurs in diabetics, immunocompromised patients, or patients with urinary tract obstruction. The hallmark of this condition is the presence of air in the renal parenchyma or renal pelvis. On sonography, air is seen as echogenic areas but may be missed at times. Occasionally, differentiation of echogenic foci from calculi may be difficult. CT is far more sensitive than sonography or plain X-ray in detecting air which is seen as jet black specks. Gas may also be seen in the perinephric regions.

ACUTE RENAL FAILURE

The question to be answered by imaging is whether the urinary system is obstructed or not. Sonography adequately answers this question where dilatation of the pelvicalyceal system is seen as the separation of the renal sinus echo. Occasionally, in acute obstruction, there may be no evidence of dilatation of the pelvicalyceal system. This may be due to the fact that the obstruction is too early to manifest, or the obstruction may have led to a forniceal rupture with leakage of fluid into the perirenal region. Therefore, the presence of perirenal fluid in acute renal failure indicates obstruction. Occasionally, there may be pre-existing dilatation of the pelvicalyceal system due to an old obstruction, and the clinician has to determine whether this dilatation is due to a new obstruction, or is due to an old lesion. In this condition, a duplex Doppler of the intrarenal vessels is very useful. An estimate of the renal vascular resistance known as the resistive index (RI) is obtained by the formula—

$$RI = \frac{\text{(Peak systolic FS – Minimum diastolic FS)}}{\text{(Peak systolic FS)}}$$

(FS stands for frequency shift).

An elevated RI is seen in fresh obstruction.[20]

In acute renal failure, due to nonobstructive causes the sonogram is usually negative or may show alterations in renal size and echogenicity. These changes however are nonspecific and not helpful as regards the etiology. A duplex Doppler sonography is however helpful in differentiating acute tubular necrosis from acute prerenal failure.[21] The RI is elevated in most patients with acute tubular necrosis, but is also raised in a fifth of patients with prerenal failure.

LIVER

Hepatic Abscess

Both CT and sonography are very useful in the evaluation of hepatic abscesses. CT is slightly superior in the detection of small abscesses. Abscesses may be solitary or multiple, small or large. Amebic abscesses have a predilection for the posterosuperior portion of the right lobe of the liver and are seen on sonography as ill-defined hypoechoic areas with a wall of varying thickness. In the early stages of an abscess, the abnormal area may be seen as an isoechoic or mildly echogenic area. Later, the abscess becomes better defined and more hypoechoic. Often there is debris present in the abscess seen as layering of echogenic material. On CT, abscesses are seen as ill-defined hypodense or nonenhancing areas with a wall of varying thickness.

Large abscesses should be subjected to sonographic or CT-guided aspirations. Of particular importance is the approach used in the aspiration of these abscesses. A liver abscess should not be approached posteriorly as the inferior margin of the posterior recess of the pleura is not known, and inadvertently the pleura may be transgressed; seepage of purulent material from the liver abscess could result in an empyema. Abscesses in the posteriosuperior quadrant of the right lobe of the liver are very difficult to tackle, and are best aspirated under CT guidance. Very large abscesses are best treated with catheter drainage as they would otherwise necessitate a long hospital stay and multiple aspirations.

Immunosuppressed patients with acquired immunodeficiency syndrome (AIDS) or those on chemotherapy may have multiple disseminated fungal abscesses—the most

common incriminating organism being *Candida albicans*. These abscesses have a relatively classical appearance on CT—a hyperdense core with peripheral hypodensity (bull's eye lesion). On sonography, the appearances vary: (1) wheel in wheel appearance with a hypoechoic center, a hyperechoic wall and a hypoechoic periphery; (2) bull's eye lesion with hyperechoic center and hypoechoic outer margin. Occasionally, these abscesses may be uniformly hypoechoic or hyperechoic.

Imaging modalities may help in the diagnosis of a number of other intra-abdominal or gastrointestinal problems in immunosuppressed patients, particularly in AIDS. Thus, cytomegalovirus infections, infections with *Mycobacterium avium-intracellulare*, or *Cryptosporidium* infections in patients with AIDS, can cause an ascending cholangitis recognizable on CT by the presence of dilated intrahepatic biliary radicles. Kaposi's sarcoma, non-Hodgkin's lymphoma may involve the gut. Splenomegaly may be related to a lymphoma. AIDS enteritis may involve the jejunum with effacement of the jejunal folds. CT is the ideal imaging modality as it evaluates visceral organs, adenopathies, and bowel loops. A CT-guided biopsy in visceral disease or in lymphadenopathy also helps in arriving at an exact diagnosis.

Liver Trauma

After the spleen and the kidney, the liver is the third most common organ likely to be injured in abdominal trauma. Most cases result from blunt trauma. The lesions can range from a small tear to a large laceration with an intrahepatic hematoma. CT is the imaging modality of choice in abdominal trauma. An acute hematoma is seen as a bright area (brighter than the liver parenchyma) on the unenhanced scan. After administration of intravenous contrast medium, the lesion does not enhance, the lesion thereby appears darker than the liver.

Peritonitis

Diagnosis of peritonitis is nearly always clinical, the role of imaging being merely to demonstrate: (1) free fluid in the peritoneal cavity; (2) intraperitoneal abscess; (3) the etiology of peritonitis. Sonography is usually adequate to detect free fluid. Small amounts of fluid may be seen in the hepatorenal pouch and/or in the pelvic cul de sac. When there is a large amount of fluid, the liver, spleen and bowel loops are pushed to the center of the abdomen, with the fluid being peripheral. The fluid if not grossly infected may be sonolucent. Severely infected fluid is echogenic with loculations or debris.

Intraperitoneal abscesses occur due to a variety of causes. Most occur between the transverse colon and the diaphragm. Nearly 60% of these are on the right side, 15% bilateral and 25% on the left. Abscesses can occur anywhere in the abdomen or pelvis, and are often distant from the site of perforation or primary pathology. Therefore, the whole abdomen and pelvis need to be imaged in detail when looking for intraperitoneal abscesses. Sonography has been found to be superior to CT in evaluating subphrenic abscesses as these tend to be more plaque-like, spreading along the surface of the liver or spleen. Therefore, a coronal form of imaging is useful to demonstrate these plaque-like abscesses, and determine their relation to solid visceral organs. MRI scanning (which gives good coronal images) is also a useful modality in localizing these abscesses. However, the ability of MRI to image the rest of the abdomen is poor. CT is far superior to sonography for detection of abscesses in other portions of the abdomen/pelvis, as well as interloop abscesses, which may be missed on sonography. When a search for an intra-abdominal abscess is undertaken with CT scan, it is very important that a large quantity of oral contrast (1.5–2 L) is given to the patient and this is supplemented with intravenous contrast. This is because dilated fluid-filled bowel loops can mimic abscesses and vice versa. False-negative or false-positive results may at times occur when there is inadequate opacification of the bowel loops.

On sonography, abscesses appear as relatively well-defined hypoechoic lesions with or without a layering of debris in the collection. On CT, abscesses appear as well-defined phlegmonous mass lesions which undergo central liquefaction and have thick peripheral enhancing walls. Occasionally, there may be gas within the collection indicating infection by a gas forming organisms. This is the surest sign of an abscess. The differential diagnosis of abscesses is pseudocysts, cysts, urinomas, biliomas, loculated ascites, old hematomas and necrotic tumors. The clinical setting as well as radiographic appearances helps to differentiate the varying pathologies. Differentiation can sometimes only be achieved by percutaneous aspiration.

IMAGING-GUIDED PROCEDURES

Over the years, technological improvements in imaging modalities and catheter design have considerably helped to improve the safety, simplicity and effectiveness of imaging-guided procedures. This has therefore led to a greater acceptance of these procedures.

Drainage of Localized Intra-Abdominal Suppuration

Drainage of an intra-abdominal abscess is commonly performed in critically ill patients under either US or CT guidance.

Sonography is also useful for percutaneous transhepatic drainage, cholecystostomy and percutaneous nephrostomy. These procedures may be performed under sonographic guidance or with the help of fluoroscopy.

Contraindications

Contraindications for drainage of a collection are: (1) lack of a safe access route, i.e. through the bowel or vascular structures; (2) associated coagulopathy; (3) subdiaphragmatic abscesses which cannot be approached without traversing the pleura; (4) poorly formed abscesses–such as pancreatic necrosis; (5) multiloculated and multicompartment abscesses.

Methods of Drainage

There are two main methods employed in the insertion of drainage tubes—one being the Seldinger technique and the other the Trocar technique. In the Seldinger technique, a 22 gauge needle is introduced first and fluid is aspirated to confirm that the needle is in the collection. Once this is confirmed by imaging, the needle is removed and dilators passed over the guidewire to dilate the tract. Dilators (from size 6 Fr upward) are used progressively in increments of 2 Fr and constantly watched under fluoroscopy. Depending on the size of the pigtail catheter, the track is dilated to a 2 Fr size above the size of the catheter required. Generally for thin fluid collections or bile an 8 Fr size catheter is adequate, while for thicker collections like pus 10–13 Fr is necessary. For even thicker material a catheter up to about 24 Fr can be inserted. The catheter is advanced over the guidewire into the collection. Once in the collection the guidewire is removed and fluid or pus aspirated and drained via the catheter. Following complete aspiration, contrast is injected and a cavitogram is performed to ensure that the cavity is totally drained, as well as to see if there are any other pockets of collection or fistulas opening in to the GI tract. The catheter is then secured to the skin. An important point to note is that at all times the guidewire should be held at the skin site so that it is not dislodged from the collection.

The Trochar technique is a very convenient technique as it does not involve a guidewire, and hence the chances of the guidewire slipping are absent. Also it is a rapid technique and can be performed under sonography or CT guidance. The main limitation is that only catheters up to 8 of 10 or 12 Fr can be used. However, this thickness has been found to be more than adequate for drainage of thick pus. In this technique, the pigtail catheter is loaded on the needle. The needle is introduced into the collection, the stylet removed, pus aspirated and the pigtail advanced over the needle into the collection. The pigtail coils in the collection and the needle is then removed. The pigtail is then fastened to the skin and a drainage bag is attached.

When selecting the guidance system for drainage, it is important to keep the following points in mind: (1) note if the patient can be transported; (2) check regarding availability of the equipment; (3) check whether adjacent structures are adequately visualized; (4) localize the anatomical area to be aspirated or drained. The most important factor is safety and accuracy of the guidance system. CT is the best modality for guidance as it can visualize the extent of the abscess, visualize the bowel, lung and free air, display the entire abdomen, visualize through postoperative drains and dressings, and can confirm accurate and adequate drainage. The main disadvantage of CT is the need to transport the patient to the CT scanner suite.

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CHAPTER 12

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GENERAL CONSIDERATIONS

Computerized tomography (CT) scanning was introduced in the mid-seventies and enabled a direct visualization of the brain parenchyma, ventricles and cisterns. CT imaging, thus replaced invasive diagnostic radiology techniques such as air encephalography, ventriculography and cisternography; it also decreased the use of carotid/vertebral angiography. Magnetic resonance imaging (MRI) was introduced in the mid-eighties, and this became another important modality in the evaluation of the central nervous system (CNS). MRI has a better intrinsic contrast of images and a higher sensitivity for pathologic changes on T2-weighted images (T2WI). One of the important advantages of MRI over CT is its ability to image soft tissues in the absence of artefacts from overlying bone. This makes MRI the modality of choice in evaluating the brainstem, posterior fossa, extra-axial regions and the spinal cord.

The advantages of CT over MRI are that bony abnormalities, calcification and hyperacute hemorrhage are well detected. Another important advantage is that critically ill patients can be more easily monitored during CT than during MRI. Though MRI compatible ventilators, pulse oximeters and respiratory monitors have now been introduced, they are not widely available, and further in the event of a cardiorespiratory arrest, the patient needs to be removed from the MRI room because defibrillation and ECG monitoring cannot be performed close to the magnet. MRI is contraindicated in patients with cardiac pacemakers, implanted auto defibrillators, thermodilution Swan-Ganz (S-G) catheters, and cochlear implants.[1] Implanted drug infusion pumps may also stop during imaging.[2] Ferromagnetic objects in a patient may move or become dislodged producing damage to the patient, or artefacts in the images. The majority of intracranial aneurysmal clips are ferromagnetic; movement of these clips in the MRI can have disastrous consequences. Non-ferromagnetic clips are now available. However, most hemostatic vascular clips, staples, carotid artery clamps (except Poppen-Blalock carotid artery clamp),[1] wire sutures, vascular access ports, plastic endotracheal tubes, chest tubes, catheters (except S-G catheters), orthopedic devices, prosthesis, prosthetic heart valves (except Starr-Edwards 6000 valve), intravascular coils, stents and filters are safe in the MRI. Most bullets are non-ferromagnetic[3] (in doubtful cases, a similar bullet is taken to the MRI suite and checked). Another disadvantage of MRI is the longer examination time as compared to CT, though newer MRI machines with echoplanar MRI are as fast as or even faster than CT.

With the advent of carotid Doppler and MRI angiography, and spiral CT angiography, the use of angiography has reduced considerably. However, none of these techniques can totally replace angiography, as angiography is required prior to surgery in carotid stenosis, intracranial aneurysms and angiomatous malformations. Cerebral angiography is also being now used for interventional purposes—carotid angioplasty, embolization of aneurysms and angiomatous malformations.

HEAD INJURY

Computerized tomography is far superior to MRI in the evaluation of patients with acute head injury as it is more sensitive than MRI in the detection of acute hemorrhage and fractures. Further, patients who have polytrauma require CT for imaging the thorax and abdomen; CT head can be done at the same time. MRI is useful in the evaluation of subacute/chronic subdural hematomas, and is far superior in the

evaluation of diffuse axonal injury. A plain X-ray of the skull can only demonstrate the presence of a fracture, and help determine if the fracture is depressed. If there is a fracture, a CT must be performed. A basal fracture may not be seen on a skull X-ray. However, air in the subarachnoid space points to a fracture of the base of the skull. Other areas that can be evaluated for fractures on a plain X-ray are the orbit/paranasal sinuses and upper cervical spine.

On CT, fractures appear as linear breaks in the calvarium. A depressed fracture is seen as a bony fragment compressing the underlying brain. It is important to see if there is any underlying hematoma or hemorrhagic contusion, because elevation of the fragment can cause an increase in the size of an underlying hematoma.

Extradural Hematoma

An extradural hematoma occurs due to a tear of an artery traversing between the dura and the calvarium, resulting in a hematoma which strips the dura from the inner table of the skull. There is usually an associated overlying fracture, the common sites being the frontal and temporal regions near the branches of the middle meningeal artery. On CT, extradural hematomas are seen as very hyperdense, well-defined collections, which have a biconvex or lenticular appearance. They may cross the midline as they are limited only by sutural margins. Internally they may contain areas of lower attenuation due to presence of unclotted blood. These hematomas tend to be brighter than other hemorrhages as there is no mixing with cerebral spinal fluid (CSF). Of particular importance are posterior fossa epidural hematomas, as they have a mortality rate of 37–69%.[4] Fortunately, they are relatively uncommon.

Subdural Hematoma

Subdural hematomas are the most common of post-traumatic intracranial hematomas. They occur due to a tear of a bridging vein in the subdural space resulting in a hematoma between the dura and arachnoid. Rarely, they may occur in the posterior fossa due to a tear of a venous sinus. The most common cause of a subdural hematoma is head injury. However, rarely they may occur following shunt placement, coagulopathy, arteriovenous malformations or aneurysmal bleeding. Subdural hematomas are concavo-convex in shape conforming to the contour of the brain; they are limited by the falx cerebri and therefore do not cross the midline but may extend into the interhemispheric fissure. It is important to note that subdural hematomas lying over the convexity below the frontal/occipital lobes, or above/below tentorium are much better imaged by coronal scans. Subdural hematomas are classified according to their age into three types, acute (1–3 days old), subacute (3–22 days old), and chronic (more than 22 days old).

Acute subdural hematomas are best imaged by CT as MRI is relatively insensitive to acute hemorrhage. These appear as crescentic high attenuation lesions causing mass effect on the ipsilateral cortex with effacement of the sulci and a shift of the midline structures to the opposite side. Rarely in severe anemia with hemoglobin less than 5 g/dL, acute subdural hematomas may appear to be of low attenuation, resembling chronic hematomas. As subdural hematomas age, they decrease in attenuation appearing in a spectrum between mildly hyperdense to mildly hypodense, with a certain proportion being isodense with brain parenchyma. Due to the minimal density differences between these hematomas and brain parenchyma they may be difficult to detect.

There are indirect signs which may help to detect a subacute or isodense subdural hematoma. These are: (1) effacement of the cortical sulci; (2) a subtle inbuckling of the gray/white matter interface on the ipsilateral side, as the brain parenchyma is displaced away from the calvarium; (3) compression of the ipsilateral ventricle. Rarely but not uncommonly bilateral isodense subdurals may be present; as the ventricular system is compressed from both sides it appears very small and pinched. In doubtful cases, intravenous contrast may be used as this enhances the membrane of the subdural hematoma along with the cortex of the brain, thereby helping to define the subacute subdural easily. If doubt still exists, an MRI is warranted. Due to the presence of methemoglobin in subacute subdural hematomas, these hematomas appear very bright on MRI resulting in very easy depiction.

Chronic subdural hematomas are often not accompanied by a clinical history of head injury as the patients are usually elderly, alcoholic or have psychiatric problems. On CT, they are seen as crescentic hypodense fluid collections causing effacement of the sulci, shift of the midline structures and compression of the ipsilateral ventricle. On MRI these appear as hypointense on T1-weighted images (T1WI) and hyperintense on T2WI. These may be difficult to differentiate from subdural hygromas, which appear similar on CT and MRI. The only differentiating factor is the presence of a membrane, which is present in hematomas. Occasionally, a chronic subdural may mimic an acute subdural due to rebleeding into the subdural.

Contusions

Contusions occur due to a shearing injury and are most commonly seen in the anterior portions of the frontal and temporal lobes. They may be hemorrhagic or non-hemorrhagic. They may be small or very large causing significant mass effect, and are often multiple and bilateral. On CT they appear as ill-defined hyperdense areas with peripheral hypodensity, or multiple ill-defined hyperdense areas, which tend to get confluent with peripheral hypodensity. The non-hemorrhagic contusions appear hypodense and are better detected on MRI than CT.

Magnetic resonance imaging is far superior in the evaluation of diffuse axonal injury especially in patients with severe post-cognitive disorders in whom the CT is often negative. These axonal injuries are seen as multiple ovoid/round areas of altered signal intensity in the corpus callosum, centrum

semiovale and at the gray/white matter interfaces. Eighty percent of these lesions are non-hemorrhagic. The cortex is usually spared but larger lesions may involve the cortex. Occasionally these lesions are seen on the dorsolateral aspect of the brainstem and the cerebellum.

A rare form of subcortical hemorrhage is seen with focal areas of hemorrhage in the upper brainstem, basal ganglia, thalamus and around the third ventricle. Patients with these findings are usually comatose, have a low Glasgow Coma Score, and often die early.

Stroke

The primary purpose of imaging in acute stroke is to differentiate a non-hemorrhagic infarct from acute hemorrhage. The modality which best meets this purpose is CT, as MRI is relatively insensitive to the detection of acute hemorrhage. Infarcts are detected earlier on MRI, as early as 6 hours after the cerebrovascular accident. Also, small lacunar infarcts in the basal ganglia, internal capsule and posterior fossa may never be seen by CT, and may be visualized only by MRI. On CT the infarcted area is seen as an ill-defined hypodense area with associated mass effect, which becomes more hypodense as it ages. In the subacute phase, the infarct may become isodense and may be missed on a plain CT. This is due to revascularization of the infarct and is known as the fogging phase. In this situation, intravenous contrast may be useful as it will demonstrate dense peripheral gyral enhancement. This is also known as luxury perfusion, which starts at 6 days and persists till 6 weeks. Flooding of an infarct with ionic contrast has been known to increase the incidence of necrosis of the infarct. Nonionic contrast however has not shown any of these adverse effects; therefore, in cases of stroke, if contrast is to be administered, nonionic contrast should be used.[5] If the infarct is deep in the brain (as for example in the basal ganglia), then instead of peripheral gyral enhancements, ring enhancement may be seen. Chronic infarcts appear as very hypodense (CSF attenuation) areas with associated gliosis.

Infarcts typically conform to a vascular territory, unless they lie between vascular territories and are known as watershed infarcts, e.g. in the frontoparietal region between the anterior cerebral artery and the middle cerebral artery, and in the parieto-occipital region between the middle cerebral artery and the posterior cerebral artery. These infarcts are commonly seen in hypoxia or due to hypoperfusion distal to a high grade carotid stenosis. Occasionally, large infarcts may be seen involving the anterior cerebral artery, middle cerebral artery territory, with or without the ipsilateral posterior cerebral artery territory or the opposite anterior cerebral artery territory. These are usually due to internal carotid artery occlusion. On MRI, an echogenic area may be seen in the internal carotid artery representing a thrombus.

On MRI infarcts appear iso- to hypointense on T1WI, and bright on T2WI. As the infarct ages, it becomes more hypointense on the T1WI. Diffusion images are particularly sensitive to detection of acute infarcts, within a few minutes of the ictus changes are observed on diffusion images. A chronic infarct is of CSF intensity on the T1WI with associated gliotic changes. When larger areas of hemorrhage are seen within an infarct, i.e. hemorrhagic infarct, the possibility of a venous infarct or embolic infarct should be considered. The possibility of an embolic infarct should be also considered when there are infarcts in multiple vascular territories. Venous infarcts are often hemorrhagic and do not conform to any vascular territory. They are often cortical or deep such as bilateral thalamic infarcts. MRI is useful in demonstrating an associated venous sinus thrombosis, as venous sinuses are seen as flow void areas. Thrombosis of a venous sinus replaces this flow void with isointense or hyperintense signals.

Intracerebral hemorrhage occurs most commonly in hypertensive patients due to rupture of a small deep vessel. There are five typical sites, basal ganglia, thalamus, gray/white matter junction, cerebellum and pons. On CT, hemorrhage is seen as a confluent high density area with mass effect and edema. Progressive expansion of the hematoma may cause hydrocephalus or cerebral herniation. There may be associated intraventricular or subarachnoid extension of the hemorrhage. As the hemorrhage resolves the clot becomes smaller, and the edema, mass effect and density of the hematoma become less. In this subacute stage, if intravenous contrast is administered there may be ring enhancement of the capsule or hematoma. In the chronic stage, only a gliotic area is seen with no enhancement. The appearances of hemorrhage on MRI are very complex as they depend upon the paramagnetic effects of the blood degradation products. The blood degradation products are oxyhemoglobin, deoxyhemoglobin, intracellular and extracellular methemoglobin, hemosiderin and ferritin. These are serially formed as the hematoma evolves. Hyperacute hemorrhage (first 24 hours) mainly consists of the first breakdown product oxyhemoglobin, which has no paramagnetic properties; it may not be detected by MRI at all, or may be hypointense on T1WI and hyperintense on T2WI, thus resembling an infarct. Therefore, in the acute stage of a stroke, a CT and not an MRI should be performed, as only a CT will detect a hemorrhage.

Deoxyhemoglobin, intracellular and extracellular methemoglobin, hemosiderin and ferritin have relatively typical appearances. Deoxyhemoglobin appears hypointense on T1WI and more hypointense on T2WI. Methemoglobin appears hyperintense on T1WI, the appearance on T2WI depending on whether the methemoglobin is intra- or extracellular. Intracellular methemoglobin is dark or hypointense, whereas extracellular methemoglobin is bright or hyperintense on T2WI. Hemosiderin and ferritin are similar to deoxyhemoglobin; hypointense on T1 and becoming more hypointense on T2WI, with some associated blooming due to paramagnetic effects.

A significant number of strokes occur as a result of a shower of emboli from atherosclerotic disease at the carotid bifurcation. Carotid endarterectomy is currently recommended in cases of symptomatic high grade carotid stenosis to prevent a stroke. The gold standard for evaluating

carotid stenosis is angiography. Duplex color Doppler, MRI angiography and spiral CT angiography are noninvasive imaging techniques, which are proving very useful in the evaluation of carotid stenosis. These are essentially used as screening techniques. Doppler ultrasound is the most widely used screening modality. Its limitations are that it is operator-dependent resulting in a wide variability of interpretation. Tortuous carotid arteries may in addition cause diagnostic problems, and difficulties may arise in differentiating subtotal from total occlusion. Color Doppler sonography is used to determine the sites of flow abnormality and grade the severity of stenotic lesions.[6]

Magnetic resonance (MR) angiography has been recently demonstrated to be a sensitive noninvasive tool in the diagnosis of internal carotid artery stenosis. The major advantage of MR angiography is that it displays the carotid bifurcation anatomy in a format similar to carotid angiography. The degree of stenosis may however be overestimated by both MR angiography, as well as carotid Doppler in a non-proportional manner.[7] Therefore, a conversion factor cannot be calculated to correct this overestimation. Arteriography is a road mapping procedure; in addition it can detect tandem lesions such as intracranial stenosis and stenosis of the origin of the carotid artery. Recently it has been proposed that a combination of color Doppler and MR angiography can almost totally replace the need for angiography. In addition to lowering the preoperative diagnostic costs, the use of color Doppler and MR angiography reduces the complication rate to nearly nil. This has been countered by the recent development in angiography of digital subtraction angiography (DSA), which involves the use of thinner catheters, and the use of nonionic contrast medium. The use of DSA has helped to reduce the complication rate from 1–4% with traditional angiography, to 0.09–0.3%.[8]

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) occurs following rupture of an aneurysm, arteriovenous malformation, or due to trauma. A CT scan is very sensitive in detecting SAH, which is seen as hyperdensity in the sylvian fissures, the interhemispheric fissures, and along the cortex or basal cisterns. Some amount of blood may also be seen layering in the ventricles. It must be remembered that 10% of SAH may have a negative CT and if the clinical suspicion for SAH is high, a lumbar puncture is mandatory for diagnosis.

Following the demonstration of SAH, a DSA is required to detect an aneurysm. The common sites for aneurysms are at the junction of the anterior cerebral artery/anterior communicating artery, bifurcation of middle cerebral artery and junction of internal carotid artery and posterior cerebral artery. If an aneurysm is detected, it is important to demonstrate the neck of the aneurysm for surgical purposes. MRI can detect aneurysms a small as 3 mm in diameter. As flowing blood is seen as a flow void on MRI, an aneurysm appears as a circular flow void area. A partially thrombosed aneurysm is seen as a signal void area with a peripheral thrombus. This is important as on angiography only the signal void portion, i.e. the patent lumen is demonstrated. Following surgery or in the follow-up of SAH patients, a CT is necessary to monitor ventricular size, strokes (due to vasospasm) or re-bleeding. The presence of a clot helps to localize the site of an aneurysm.

Angiomatous malformations are best evaluated by MRI where they are seen as serpiginous/curvilinear signal void areas. There may be associated areas of hemorrhage or brain atrophy due to the steal phenomenon. CT scan with contrast can demonstrate enhancing curvilinear/serpiginous areas with large draining veins and feeding arteries. Angiography is useful to provide a vascular map of the arteriovenous malformation with special reference to feeding/draining vessels. This information is necessary prior to embolization/radiotherapy or surgery.

Central Nervous System Infections

Both CT and MRI are extremely useful in the evaluation of CNS infections; however, MRI is more sensitive than CT in the evaluation of both meningeal and parenchymal inflammation. Intravenous contrast enhancement is mandatory with CT and provides valuable information in an MRI scan as well.

Meningitis

Imaging in bacterial and viral meningitis is usually negative. Occasionally, leptomeningeal enchancement with intravenous contrast may be seen along the convexity of the brain. In granulomatous diseases like tuberculous meningitis, sarcoid and fungal meningitis, intravenous contrast enhanced CT or MRI may demonstrate dense enhancement in the region of the basal cisterns. The main role of imaging in meningitis is to detect complications such as communicating hydrocephalus, cerebritis, abscess, subdural effusion/empyema, ventriculitis and cortical or subcortical infarcts. Infarcts may be seen in the basal ganglia due to involvement of perforating basal vessels by associated vasculitis. Venous infarcts may occur due to venous sinus thrombosis.

Cerebritis and Abscess

There are four stages in the formation of an abscess, early cerebritis stage, late cerebritis stage, early capsule stage, late capsule stage. Most cases are detected in the late cerebritis stage or early capsule stage. MRI is considered superior to CT in the evaluation of these lesions as it is much more sensitive to subtle parenchymal changes, especially to white matter changes. On CT, cerebritis appears as an ill-defined hypodense lesion with associated mild to moderate mass effect with usually no enhancement. Occasionally, in this stage, there may be ring enhancement, which fills in later on delayed scans. On MRI, cerebritis appears as an ill-defined area, which is hypointense on T1WI and hyperintense on T2WI. Abscesses appear on CT as necrotic hypodense rounded areas with perifocal edema. After administration of intravenous contrast

the capsule/wall of the abscess enhances; the capsule is well formed on the cortical side but the ventricular side is usually thinner. This helps to differentiate abscesses from metastases, which usually have thicker, shaggier, more nodular enhancing walls. Occasionally, abscesses may be multilocular or may be associated with multiple peripheral daughter abscesses. On MRI, abscesses appear as rounded hypointense areas on T1W1 and turn hyperintense with a thin well-defined dark capsule on T2WI. There is a fair amount of perifocal edema about the abscess. As on CT, the capsule enhances with intravenous contrast on MRI.

Encephalitis

Parenchymal infections are usually most often due to a viral etiology. MRI detects changes earlier than a CT; it also provides a better estimate of the extent of the lesion, particularly when lesions involve the white matter.

Herpes simplex type I infection is an important treatable infection of the neuraxis. Herpes simplex encephalitis occurs due to latent herpes simplex virus in the Gasserian ganglion, which spreads along the trigeminal nerve retrogradely to involve the temporal and inferior frontal lobes. Rarely there may be brainstem involvement due to retrograde spread of the virus along IX, X, XI cranial nerves. MRI is far superior to CT in the detection of the subtle changes associated with herpes simplex virus (HSV) encephalitis. The changes seen on imaging are classically in the temporal and inferior frontal lobes and are seen on T2WI as ill-defined hyperintense areas. Often there is bilateral involvement of both cortex and white matter. As the lesion progresses medially, it is limited by the basal ganglia which are spared giving rise to a characteristic sharp medial margin. The disease may extend superiorly across the Sylvian fissure to involve the island of Reil. Small petechial hemorrhages are often present and are seen as hyperintensities on T1WI or hypointensities on T2WI. CT scan usually demonstrates the changes much later than MRI. The lesions are seen as hypodense areas in the temporal and inferior frontal regions. The subtle bilateral involvement seen on MRI is usually not picked up on CT. On contrast studies, there is no significant enhancement. When HSV affects immunocompromised patients, especially HIV positive patients, there may be multiple sites of involvement and it does not conform to the typical appearance as described above. Following resolution of the HSV encephalitis, necrotic and gliotic areas are seen.

Varicella zoster virus encephalitis is usually seen as brainstem encephalitis due to spread along the V and VII cranial nerves to the brainstem. On MRI, similar changes are seen on T2WI in the form of hyperintense areas in the brainstem with more involvement of white matter than gray matter. This form of encephalitis may be accompanied by vasculitis.

Cytomegalovirus encephalitis, which is usually seen in immunocompromised patients, is seen to affect both white and gray matter, with areas of altered signal intensity on T2WI. This form of encephalitis is usually accompanied by ependymitis. Post-contrast MRI reveals considerable enhancement along the ependyma. This form of enhancement may make it difficult to differentiate this pathology from primary CNS lymphomas, which also show diffuse ependymal enhancement. Usually, CNS lymphomas are accompanied by diffuse nodular enhancing lesions in the centrum semiovale and the periventricular region.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an encephalitis due to infection by JC virus (papovirus) in the immunocompromised patient. The early lesions of PML are small, round, begin in the subcortical white matter and spread to deeper white matter, becoming larger and confluent. There is sparing of the cortical gray matter giving rise to a typical scalloped appearance of the gray white matter junction. PML is usually bilateral but asymmetrical, with a predilection for involvement of the posterior centrum semiovale. Periventricular and gray matter (basal ganglia, thalamic) involvement is rare. Ten percent of cases may have lesions, which are purely infratentorial. These lesions rarely show enhancement with contrast.

HIV Encephalitis

The clinical diagnosis of HIV encephalitis usually antedates convincing radiologic evidence of the disease. On MRI, there may be diffuse areas of altered signal intensity seen in the supratentorial white matter which may be solitary or confluent. With progression of the disease, there is involvement of the cortex, basal ganglia, brainstem and cerebellum. MRI mainly displays the secondary changes of HIV encephalitis, atrophy and demyelination.

Acute Disseminated Encephalomyelitis

Magnetic resonance imaging demonstrates diffuse, ill-defined, patchy hyperintensity in the deep/subcortical white matter of the cerebrum. Occasionally, changes are seen in the midbrain, pontine and cerebellar regions, and spinal cord white matter. The lesions are few, asymmetrically distributed, without evidence of mass effect and hemorrhage. Embolic infarction, vasculitis, acute hemorrhagic leukoencephalopathy and acute multiple sclerosis need to be differentiated from acute disseminated encephalomyelitis (ADEM). Embolic infarction usually conforms to a vascular distribution. Vasculitis is not necessarily limited to white matter. There are hemorrhagic changes in acute hemorrhagic leukoencephalopathy; no hemorrhagic changes occur in ADEM. Acute multiple sclerosis and ADEM are not easily differentiated on plain MRI, but on contrast, MRI all the lesions in ADEM enhance, whereas in multiple sclerosis only active plaques enhance.

Toxoplasmosis

This is one of the most common opportunistic infections seen in patients with AIDS. Parenchymal lesions in toxoplasmosis are seen on CT as mildly hyperdense nodular lesions with

perifocal edema. On a contrast, study there is ring or nodule enhancement. These lesions are typically seen in the basal ganglia, periventricular region and the brainstem. On MRI the lesions appear iso- to hypointense on T1WI, and turn hypo- or hyperintense on T2WI with perifocal edema. With gadolinium DTPA there is ring or nodular enhancement of the lesions. Occasionally, evidence of hemorrhage may be detected within the lesions on MRI. The presence of enhancement on CT/MRI helps to differentiate active from inactive lesions. As these lesions resemble and may coexist with other parenchymal granulomas and lymphomas, the best confirmation of the diagnosis lies in the response of the lesions to antitoxoplasmal therapy. Following resolutions of the lesions, the scans may return to normal, or there may be residual gliosis. Rarely, toxoplasmosis can present as a fulminant, necrotizing meningoencephalitis in which CT/MRI can be negative.

Cryptococcosis

Intraparenchymal cryptococcal granulomas are seen typically in the basal ganglia as hypodense nonenhancing areas appearing similar to lacunar infarcts on CT, or bright areas on T2W MRI. These are in fact gelatinous masses of cryptococcal organisms inciting minimal or no inflammatory response. These may be associated with cryptococcal meningitis.

Neurocysticercosis

Disseminated neurocysticercosis is an important cause of status epilepticus in our part of the world. The cysts may be in the live, dying, dead stages, or in a combination of all three stages. Both CT and MR are very useful in demonstrating these lesions. However, MR is considered superior to CT as it is able to demonstrate the scolex better, as well as detect small live cysts thereby giving a more accurate depiction of the cyst burden. Live cysts appear as rounded CSF attenuation/intensity lesions with an eccentric scolex; no perifocal edema or cyst wall enhancement is seen with administration of intravenous contrast. Dying cysts have a similar appearance as live cysts (CSF attenuation/intensity lesions), but perifocal edema and cyst wall enhancement are present. As the scolex is often not visualized in dying cysts, they may resemble other granulomatous lesions. Dead cysts are seen as calcified foci, which are better detected on CT than MR. In disseminated neurocysticercosis, cysts are also often present in striated muscles as in the thigh, calf, tongue, myocardium, and the orbital muscles. The thigh is the commonest extracranial site; clinically, there is enlargement of the thigh muscles resulting in a pseudotumor appearance. The cysts can be demonstrated easily in these locations on imaging (CT/MR).

Spinal Cord Infarction

Infarction of the cord is most often the result of inadvertent occlusion of the anterior spinal artery during the repair of thoracic aortic aneurysms. Other causes are embolic disease, vasculitis, cardiac arrest and dissecting aortic aneurysm. MRI is the only imaging modality, which will demonstrate a spinal cord infarction, which is seen on T1W1 as a generalized swelling of the cord; on T2WI there is increased signal intensity in the involved region of the cord.

Transverse Myelitis

The role of imaging in transverse myelitis (TM) is to exclude spinal cord compression. Occasionally, in cases of TM intrinsic abnormalities may be seen in the cord on MRI. T1WI may show no change, but on T2WI ill-defined hyperintensities will be seen at the level of the affected segment. With gadolinium there may be subtle enhancement in these regions.

Spinal Trauma

Plain X-rays of the spine are extremely useful in evaluating vertebral body fractures and dislocations. However, CT provides far more information regarding the extent of the fracture, intraspinal fragments, posterior element fractures, thecal sac compression and presence of intraspinal or paraspinal hematomas. MRI is useful as it demonstrates the cord. Intrinsic cord abnormalities are not uncommon in spinal trauma and MRI is the only modality, which can demonstrate them. Intrinsic cord abnormalities may be in the form of edema of the cord due to compression by vertebral fracture; this is seen as a hyperintensity in the cord on T2WI. Other abnormalities may be the presence of hemorrhagic or non-hemorrhagic cord contusions. Hemorrhagic contusions are seen as bright areas within the cord on T1WI, and non-hemorrhagic contusions as hypointense (dark) areas on T1WI which turn bright on T2WI. Rarely there may be transection of the cord, which is best appreciated on sagittal images as a discontinuity of the cord. The presence of intrinsic abnormalities in the cord is of importance as it provides prognostic information. Extradural hematomas may occasionally cause cord compression and are best appreciated on axial MRI images as well defined hyperintense areas compressing the cord. A traumatic disc protrusion is not uncommon, and this is also well-evaluated on a sagittal or axial MR image. As bony abnormalities are well-visualized on CT, this modality has an advantage over MRI in the evaluation of posterior arch fractures, as well as in the visualization of intraspinal fragments.

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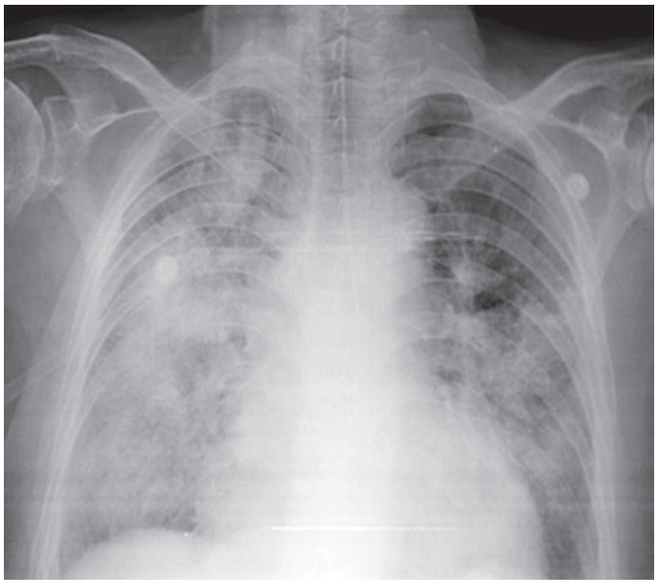
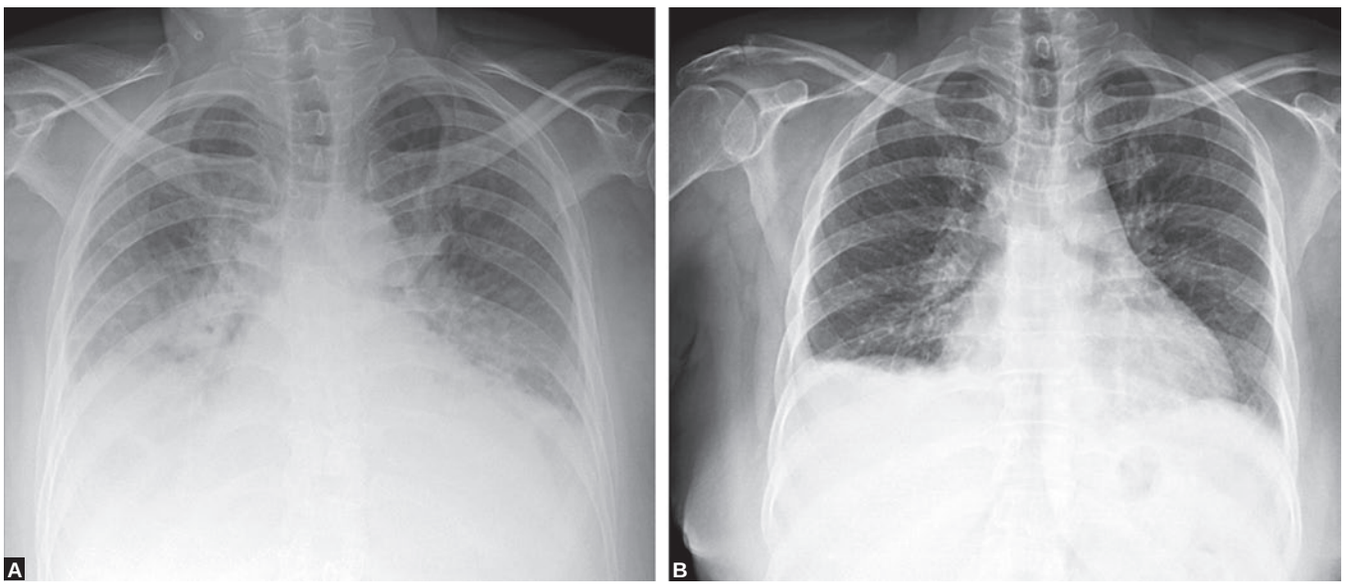


Fig. 1: Pulmonary edema. Frontal chest X-ray reveals ill-defined fluffy opacities in both lung fields, particularly right lung, representing pulmonary alveolar edema



Figs 2A and B: (A) Frontal chest radiograph reveals cardiomegaly with diffuse bilateral fluffy opacities representing pulmonary edema; (B) Demonstrates considerable clearing of pulmonary opacities following resolution of pulmonary edema

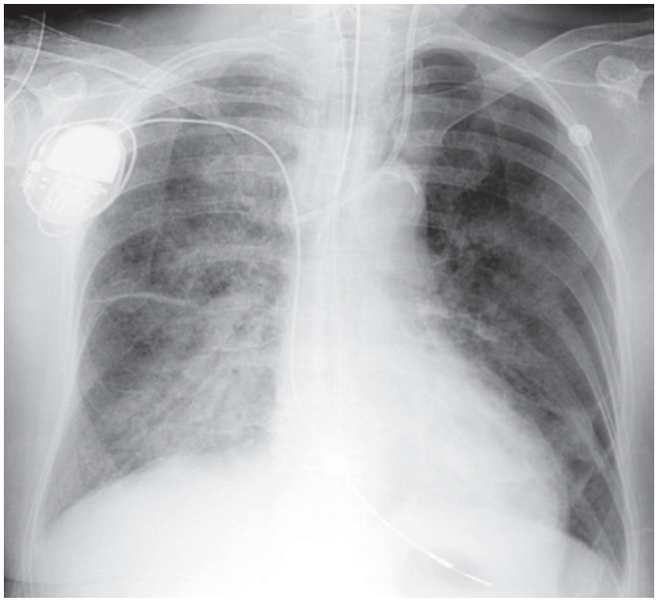


Fig. 3: Unilateral pulmonary edema. Frontal chest X-ray demonstrates diffuse fluffy opacities in right lung and minimal opacities in left lung. This unequal distribution of pulmonary edema is due to emphysematous changes in left lung

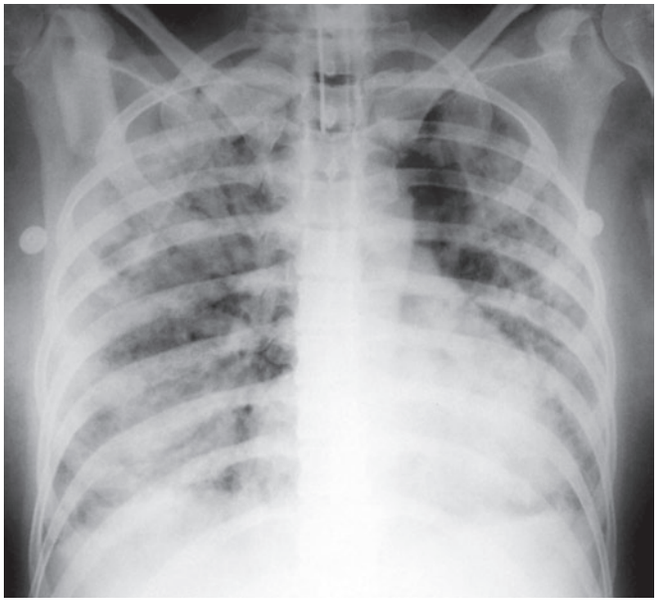


Fig. 4: Acute lung injury (acute respiratory distress syndrome). Frontal radiograph reveals ill-defined opacities in both lung fields with air bronchogram representing white out lungs due to acute lung injury

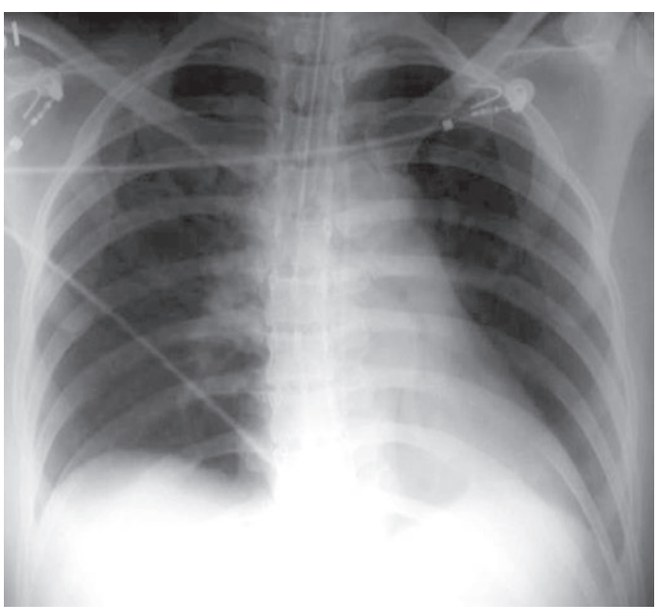


Fig. 5 : Stage I: Acute lung injury. Frontal radiograph reveals no significant abnormality

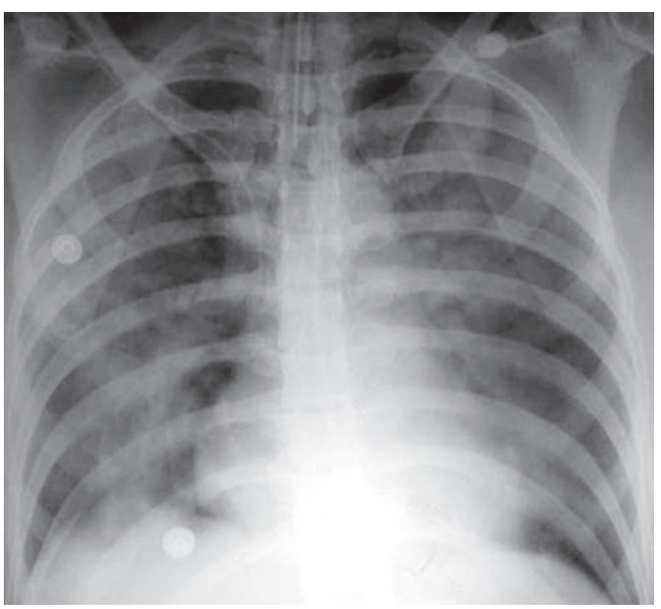


Fig. 6: Stage II: Acute lung injury. Frontal radiograph reveals ill-defined opacities in both lung fields due to acute lung injury

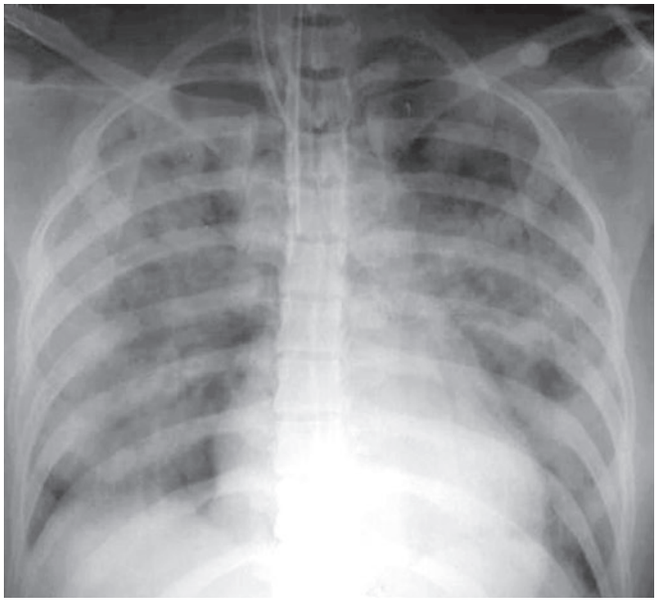


Fig. 7: Stage II: Acute lung injury. Frontal radiograph reveals progression in the ill-defined opacities in both lung fields due to acute lung injury

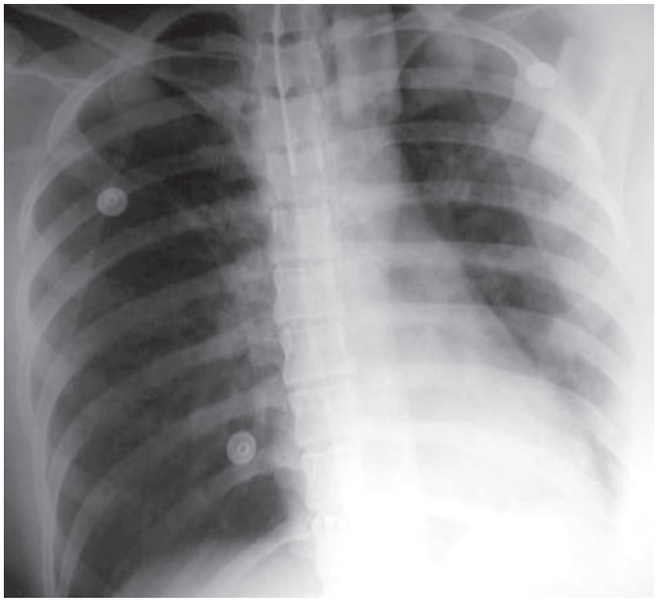


Fig. 8: Positive end-expiratory pressure (PEEP) paradox. Frontal radiograph reveals hyperinflation of lungs with apparent clearing of opacities

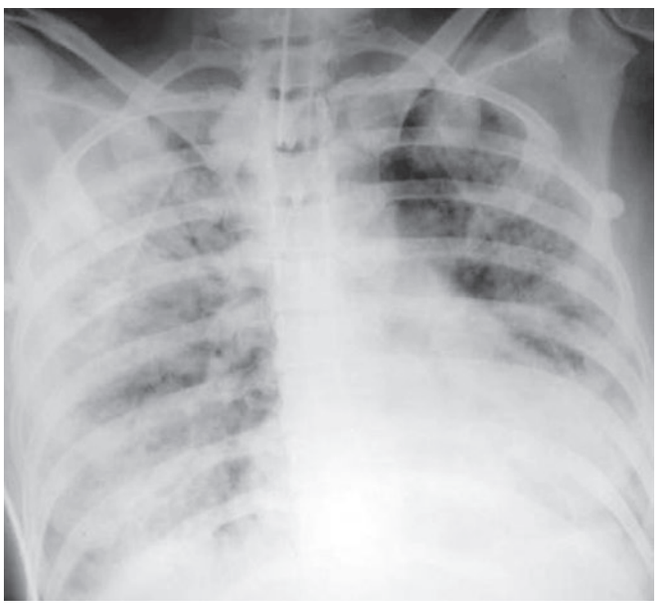


Fig. 9: Acute lung injury. Frontal radiograph reveals following removal of positive end-expiratory pressure (PEEP), opacities reappear

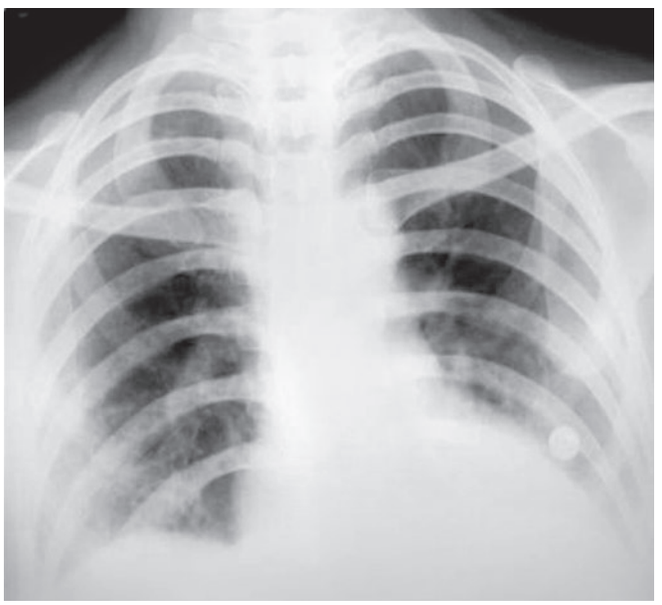
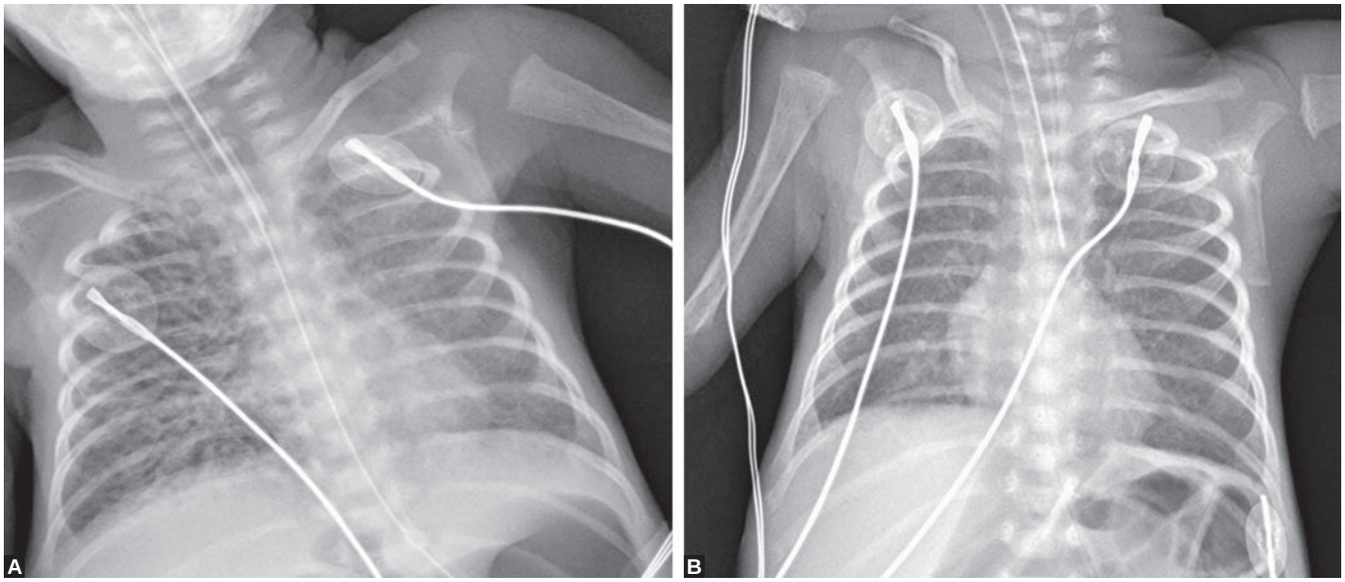


Fig. 10: Acute lung injury Stage III. Post-resolution of acute lung injury X-ray reveals no significant opacities



Figs 11A and B: (A) Pulmonary interstitial emphysema. Frontal chest X-ray reveals linear hyperlucencies representing air along bronchovascular structures and pulmonary interstitial emphysema; (B) Follow-up X-ray reveals resolution of pulmonary interstitial emphysema

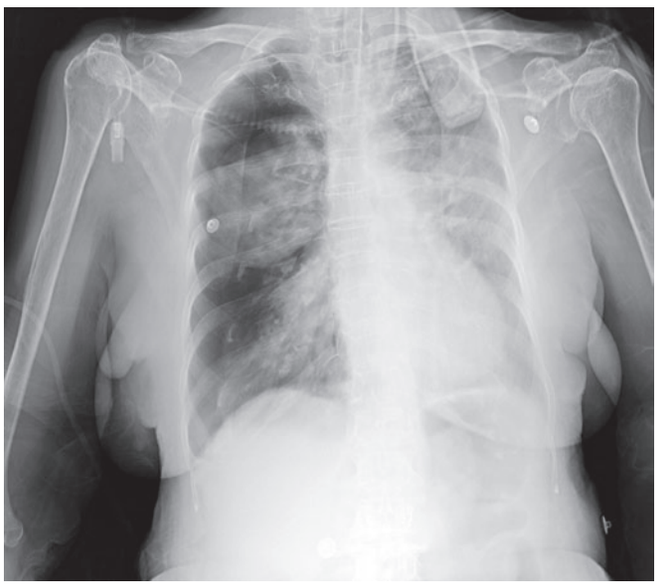


Fig. 12: Pneumothorax with acute lung injury. Frontal radiograph reveals diffuse opacities in both lung fields due to acute lung injury with a pneumothorax on the right side

Fig. 13: Aspiration pneumonia. Frontal radiograph reveals ill-defined opacities in the right mid and lower zones representing consolidation due to aspiration. There is an associated effusion

Fig. 14: Lobar pneumonia. Ill-defined consolidation seen in right lower lobe with evidence of break down

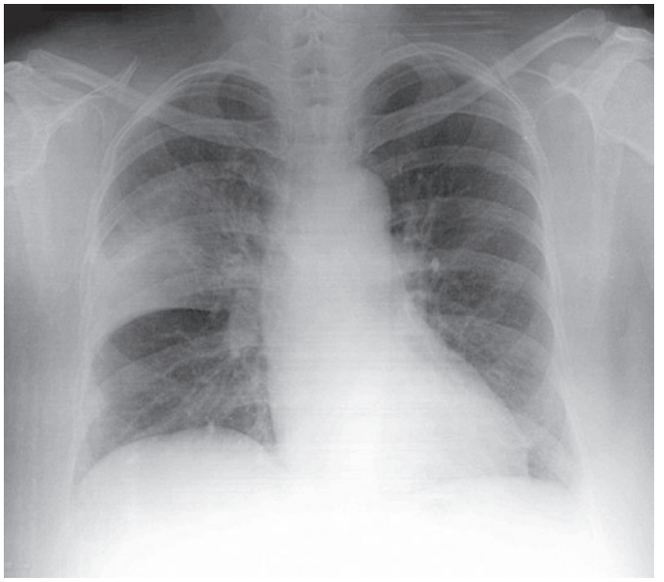


Fig. 15: Right upper lobe lobar pneumonia. Large right upper lobe consolidation limited by interlobar fissure

Fig. 16: Bronchopneumonia. Frontal radiograph presents ill-defined fluffy opacities in both lung fields as a result of bronchopneumonia

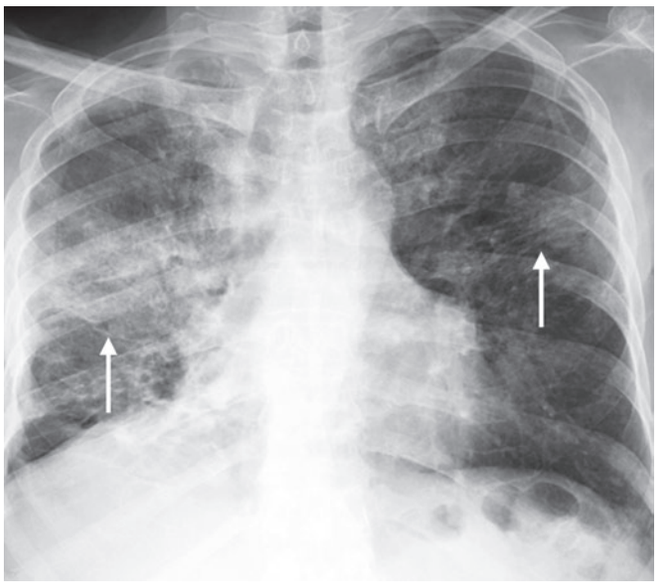


Fig. 17: Interstitial pneumonia. Frontal radiograph reveals ill-defined linear and reticular opacities which appear to conglomerate in both mid zones, more so on the right side, these would be as a result of an interstitial pneumonia

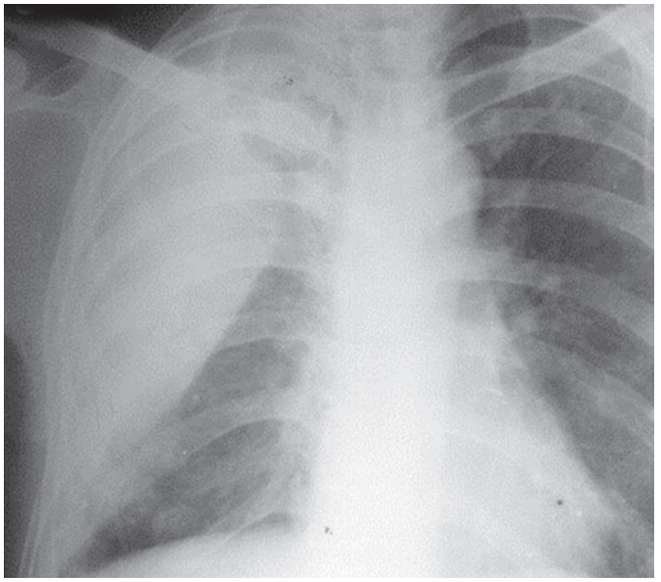


Fig. 18: Empyema. Large homogenous opacity in right hemithorax which has a wide pleural margin with obtuse angles representing an empyema

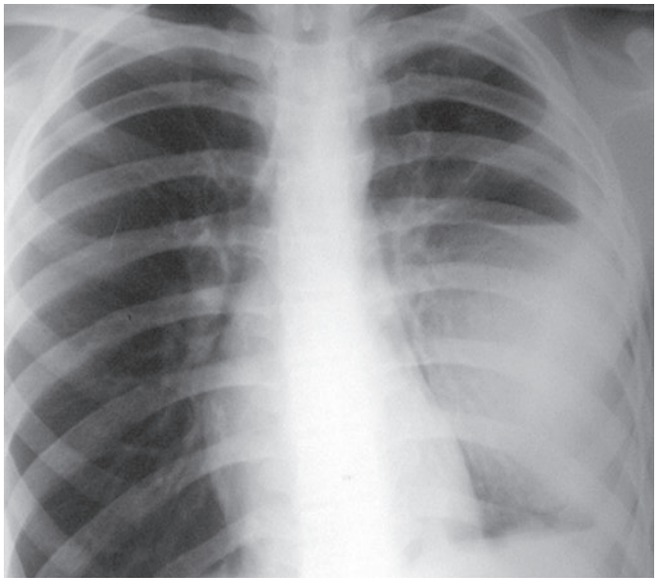


Fig. 19: Lung abscess. Frontal radiograph demonstrates a large homogenous opacity with an air fluid level representing an abscess. Note: Angle with chest wall are acute as compared to empyema with obtuse angle

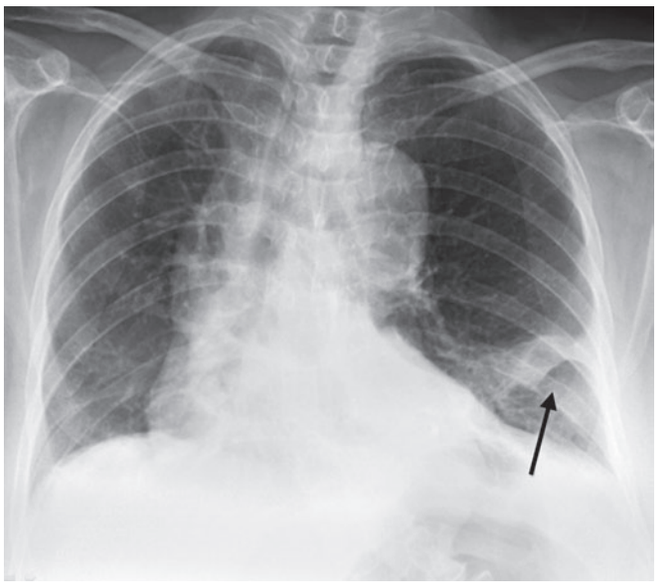
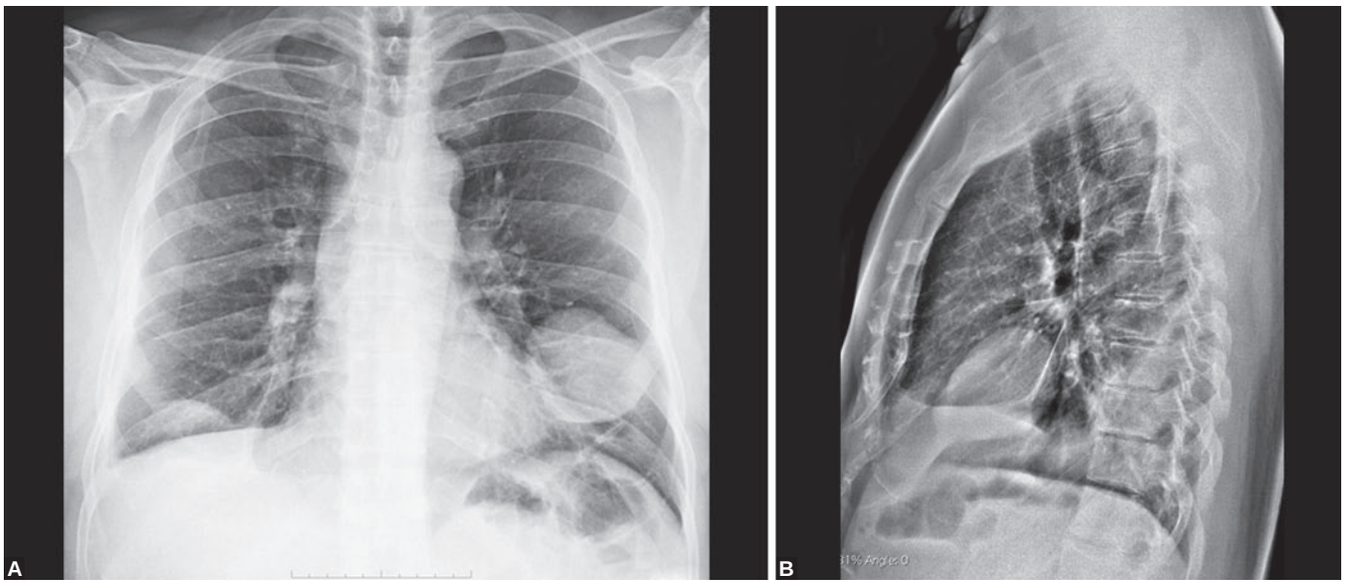


Fig. 20: Segmental atelectasis. Frontal radiograph demonstrates a segmental band-like opacity representing segmental atelectasis

Fig. 21: Pleural effusion. Frontal radiograph demonstrates a homogenous opacity in right lung base extending along right lateral chest wall representing a pleural effusion



Figs 22A and B: Loculated interlobar effusion. (A) Well-defined homogenous opacity in left lower zone; (B) Lateral chest X-ray reveals the loculated fluid collection to be in relation to the interlobar fissure indicating this represents a loculated pleural effusion in the interlobar fissure

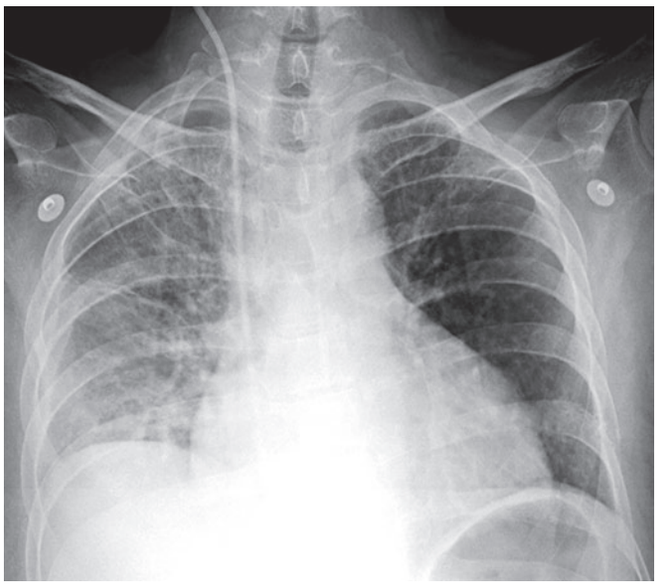
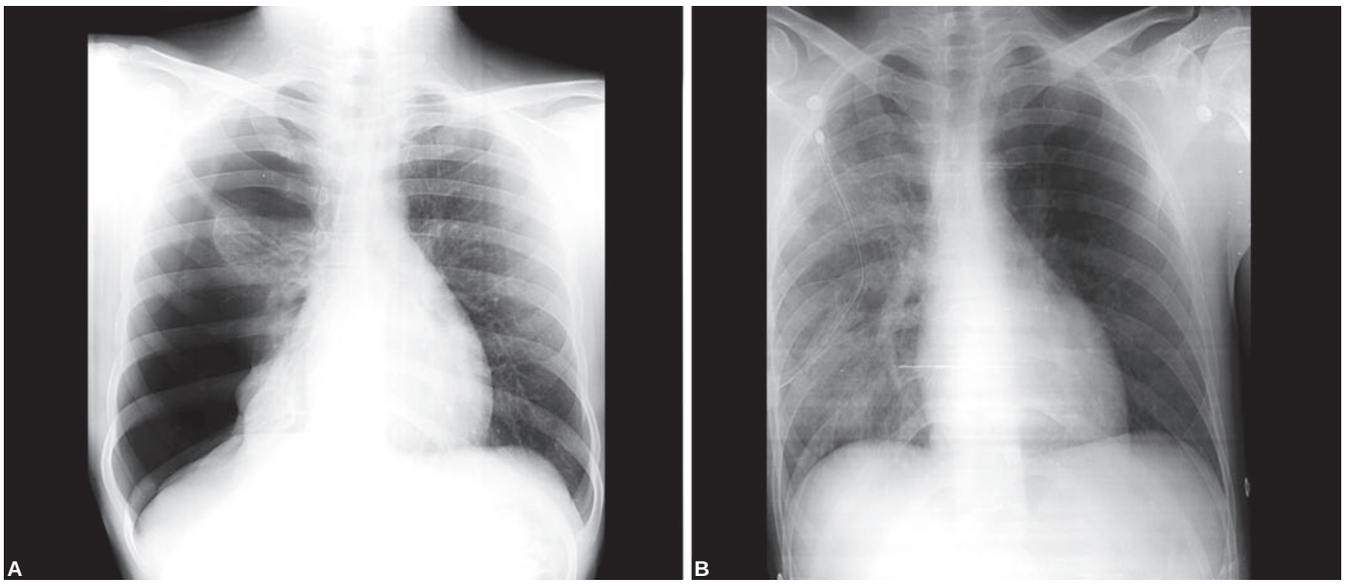


Fig. 23: Pleural effusion in supine patient. Supine radiograph reveals diffuse homogenous opacities in right hemithorax representing a pleural effusion layering along the hemithorax contributing to the opacity

Fig. 24: Subpulmonic effusion. Frontal radiograph demonstrates homogenous opacity in right base. This may be as a result of elevation of right dome of diaphragm or a subpulmonic effusion. Sonography confirmed this to represent a subpulmonic effusion



Figs 25A and B: Re-expansion pulmonary edema. (A) Frontal radiograph demonstrates a large right pneumothorax; (B) Demonstrates intercostal drain (ICD) in situ, ill-defined fluffy opacities in right lung field due to re-expansion pulmonary edema

Fig. 26: Pneumothorax. Frontal radiograph demonstrates a large pneumothorax on the left side with collapse of left lung and shift of mediastinum to right

Fig. 27: Pneumothorax. Frontal radiograph reveals ill-defined opacities in both lung fields due to acute lung injury. There is a left pneumothorax as evidenced by thin visceral pleural line as well as extensive subcutaneous edema

Fig. 28: Tension pneumothorax. Frontal radiograph reveals a large right pneumothorax with inversion of diaphragm, displacement of mediastinum to left and herniation of pneumothorax across the midline to the left

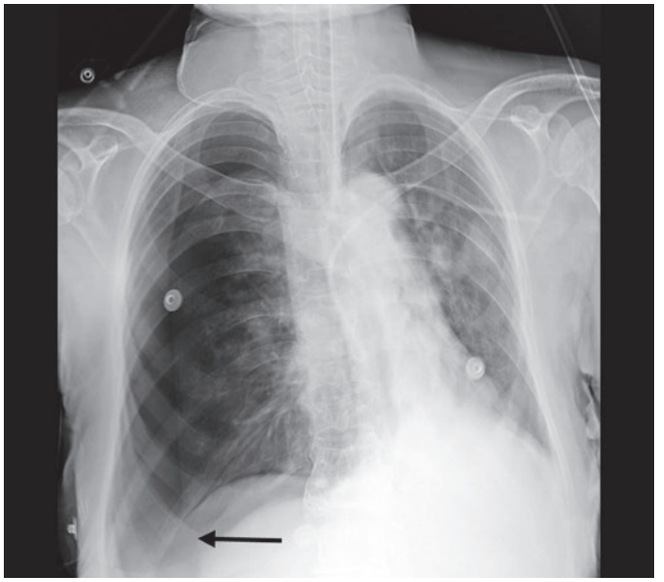


Fig. 29: Pneumothorax in a supine patient. Supine chest X-ray reveals a large lucency overlying the liver representing a pneumothorax with collection of air in the pleural space. Note shift of mediastinum to left

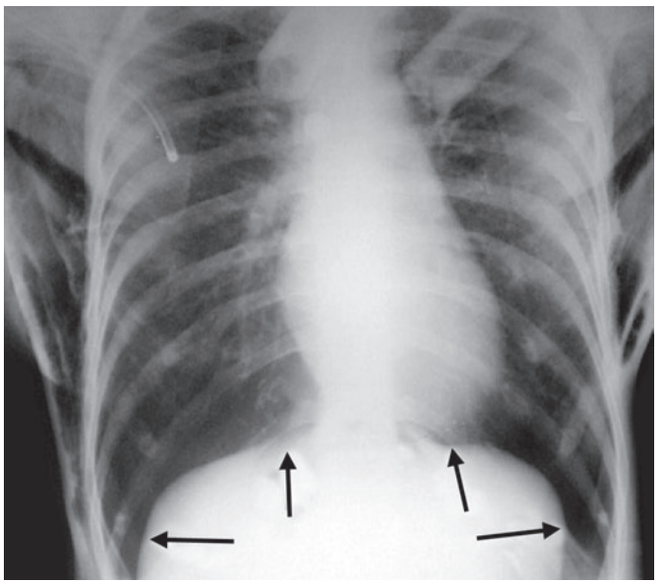


Fig. 30: Bilateral pneumothorax in a supine patient. Frontal supine chest X-ray demonstrates bilateral deep costophrenic sulcus with sharply defined diaphragm. This is because there is air collected in the pleural space

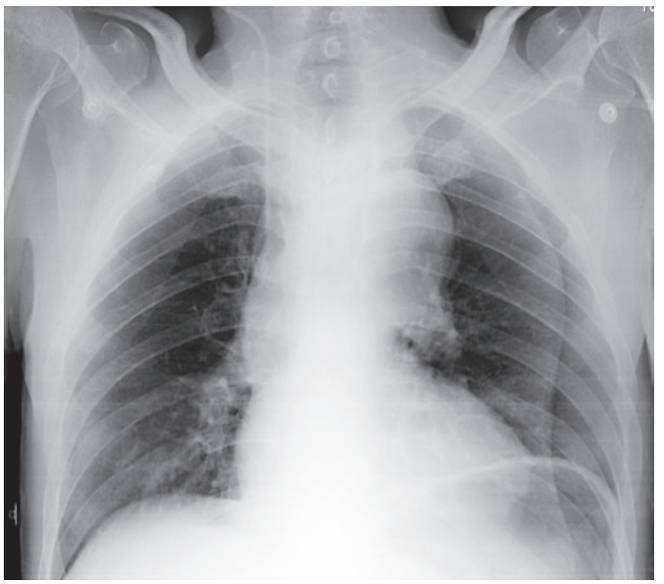
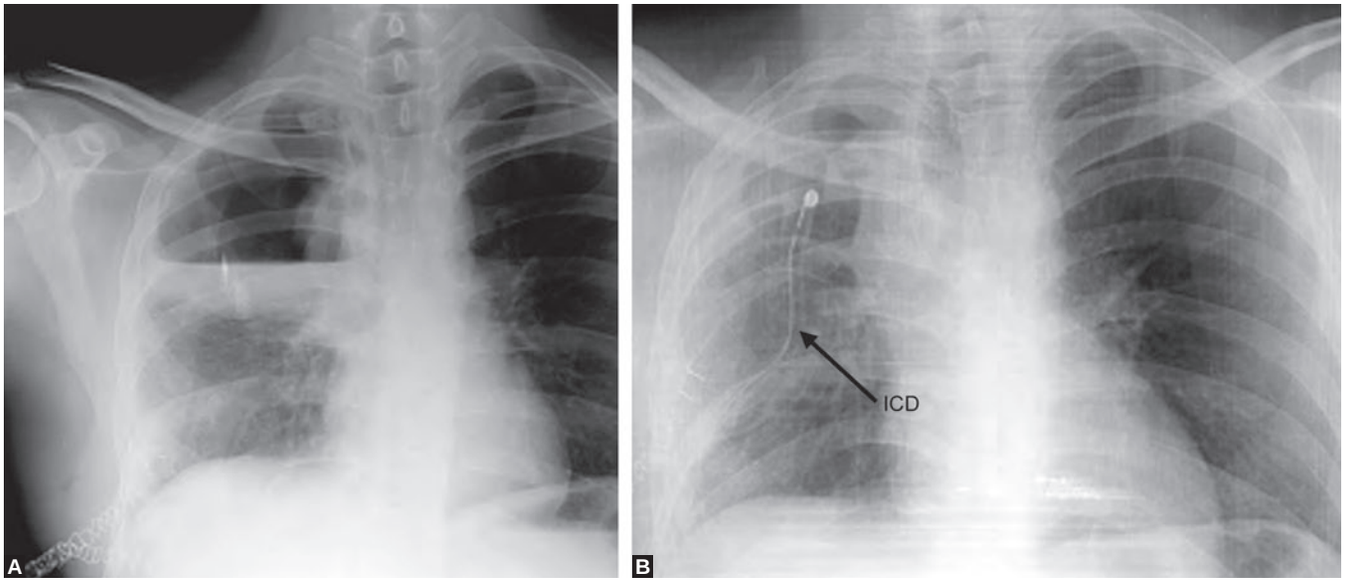


Fig. 31: Skin fold mimicking a pneumothorax. Frontal chest X-ray reveals a thin curvilinear line overlying the left hemithorax resembling a pneumothorax. This is a skin fold and not a pneumothorax as the line is seen to extend beyond the thorax over the abdomen



Figs 32A and B: Hydropneumothorax. (A) Chest X-ray demonstrates air fluid level in the right upper zone representing a hydropneumothorax; (B) This has been drained by an intercostal drain (ICD)

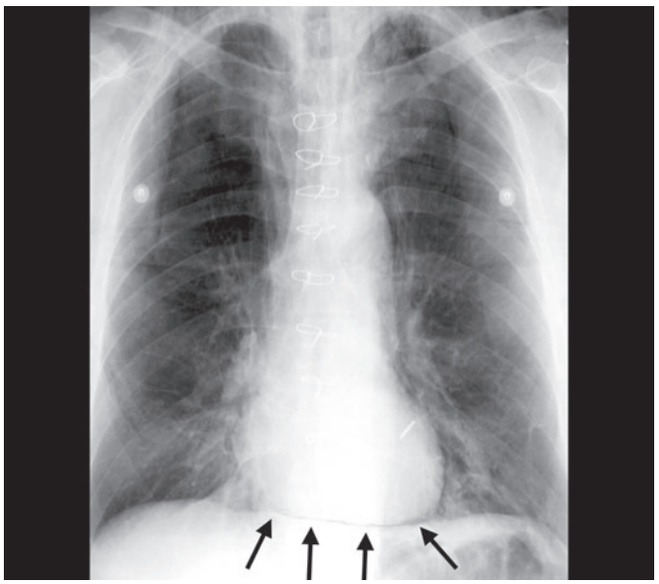


Fig. 33: Pneumomediastinum. Frontal chest X-ray demonstrates a thin air streak separating diaphragm from cardiac silhouette. These two structures usually are inseparable as both of soft tissue density, these become separable when there is air interspersed between the two as in a pneumomediastinum

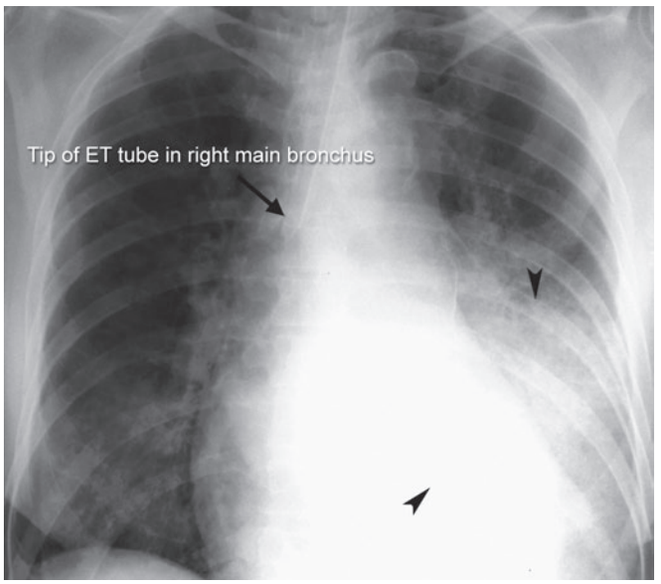


Fig. 34: Endotracheal tube in right main bronchus. Chest X-ray reveals endotracheal tube in right main bronchus. Consequently, there is hyperinflation of right lung and partial collapse of left lung

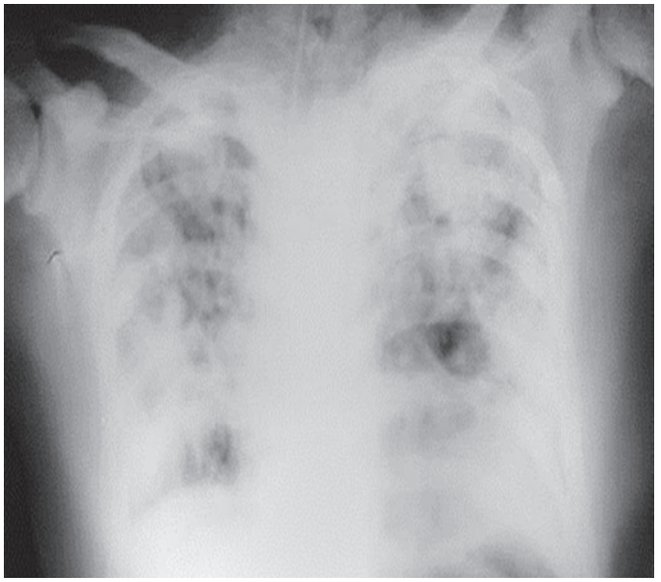


Fig. 35: Esophageal intubation. Chest X-ray reveals ill-defined opacities in both lungs. There is also hypoventilation

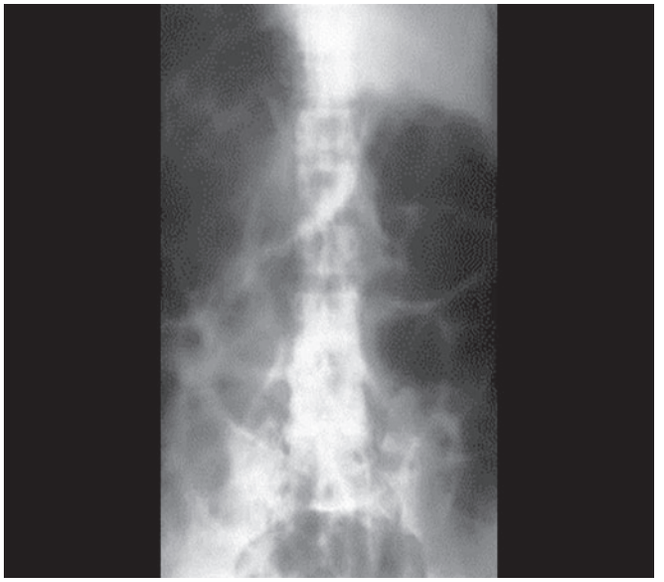


Fig. 36: Esophageal intubation. Abdominal X-ray reveals gross distension of bowel loops. Esophageal intubation has resulted in hypoventilation of the lungs and gross overdistension of the bowel

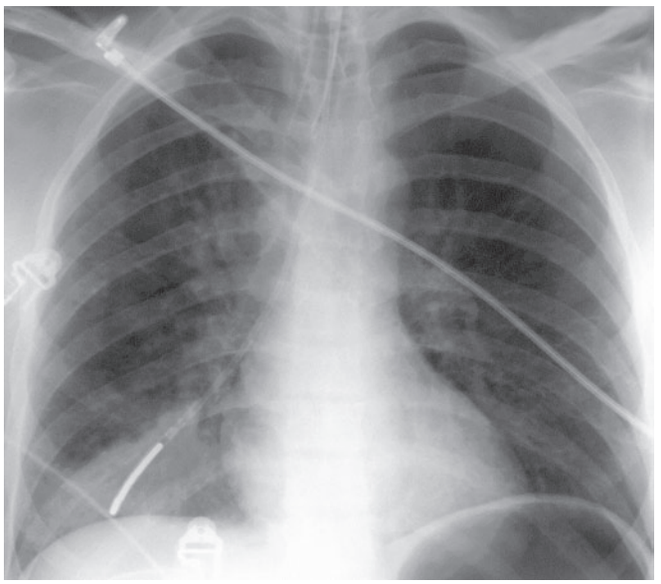


Fig. 37: Ryle's tube in right bronchus. Frontal chest X-ray reveals a Ryle's tube extending into the right lower lobe bronchus

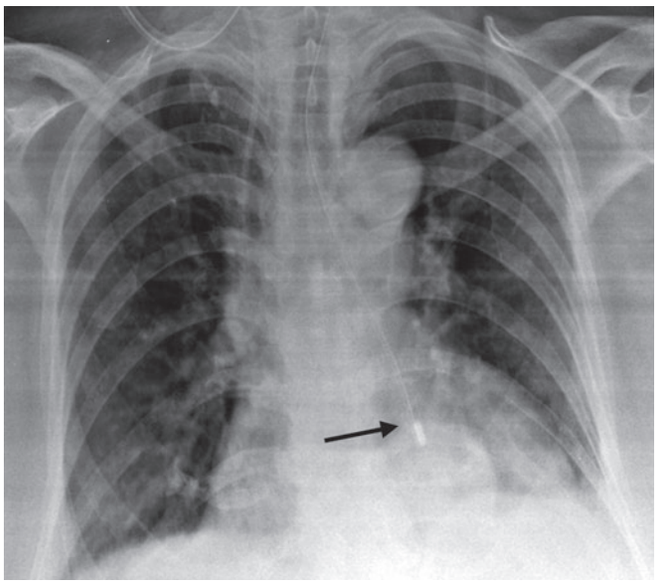


Fig. 38: Ryle's tube in left lower lobe bronchus. Chest X-ray demonstrates Ryle's tube in left lower lobe bronchus

Fig. 39: Central line too high. Chest X-ray demonstrates central line in right innominate vein. Its placement is too high

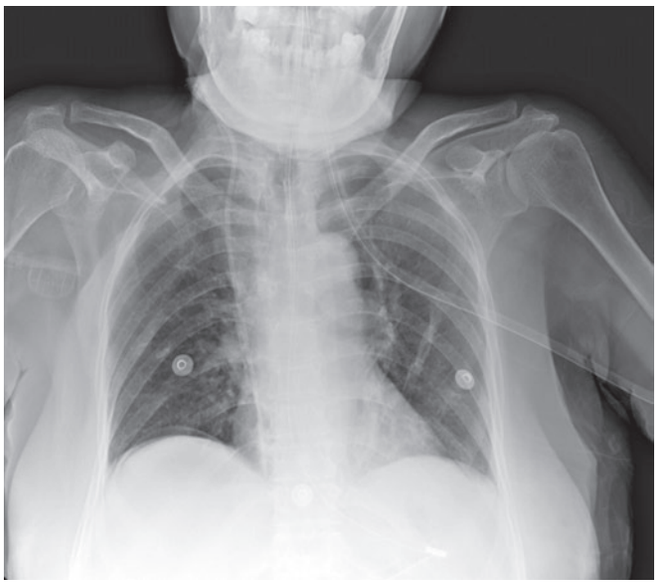
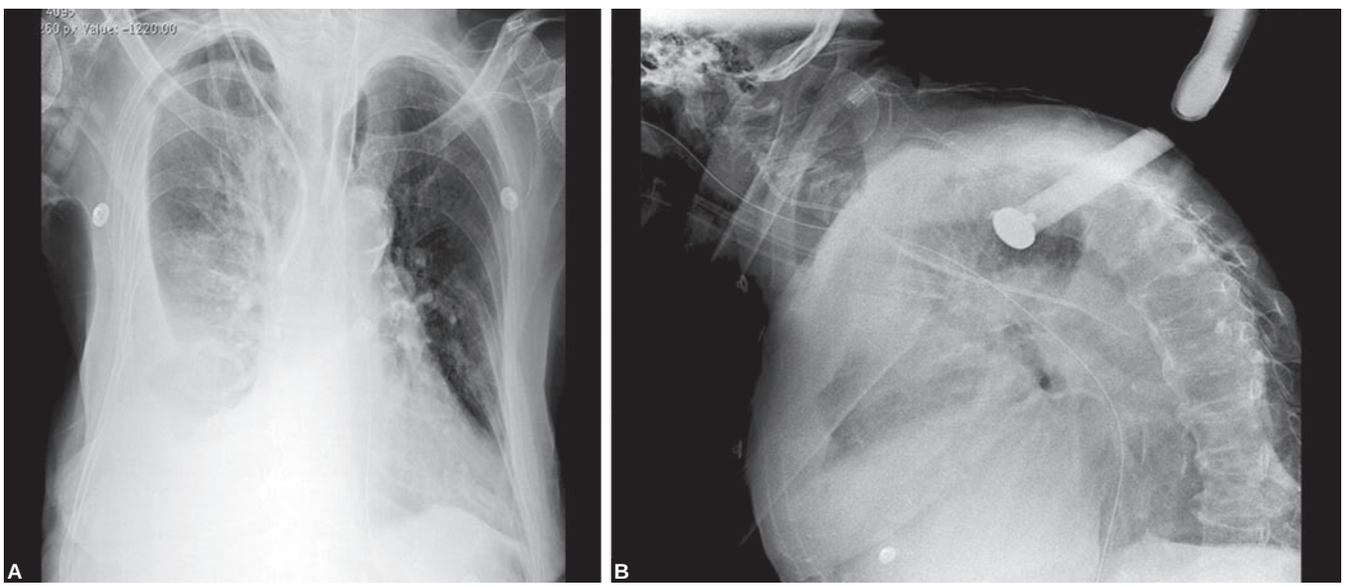


Fig. 40: Central line is placed too low. Chest X-ray reveals the central line is extending way too low into the right atrium



Figs 41A and B: Frontal chest X-ray reveals a right pleural effusion with a central line in situ. (A) The central line appears to be in good position, however the pleural space kept filling up with every infusion; (B) Lateral chest X-ray reveals tube extending posteriorly and not in the superior vena cava

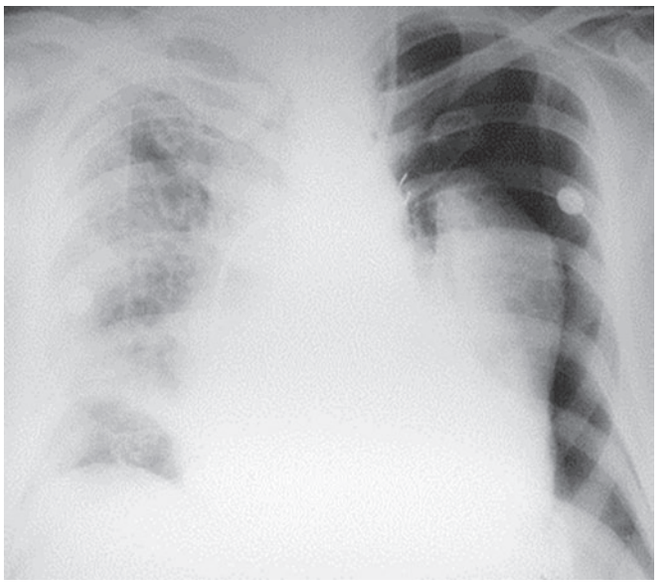


Fig 42: Post-central line pneumothorax. Chest X-ray demonstrates a central line on the left side. There is a pneumothorax on the left side, secondary to placement of central line

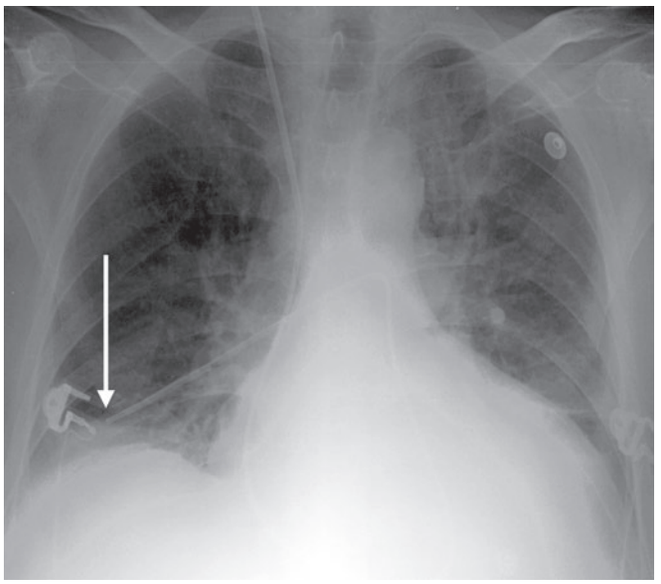


Fig. 43: Swan-Ganz catheter too far. Chest X-ray reveals Swan-Ganz catheter in right lower lobe. The tip should be within 2 cm of the hilum

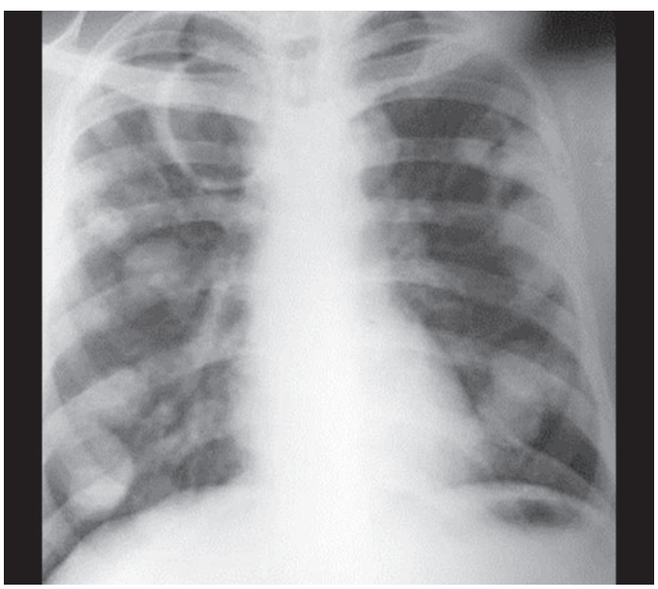
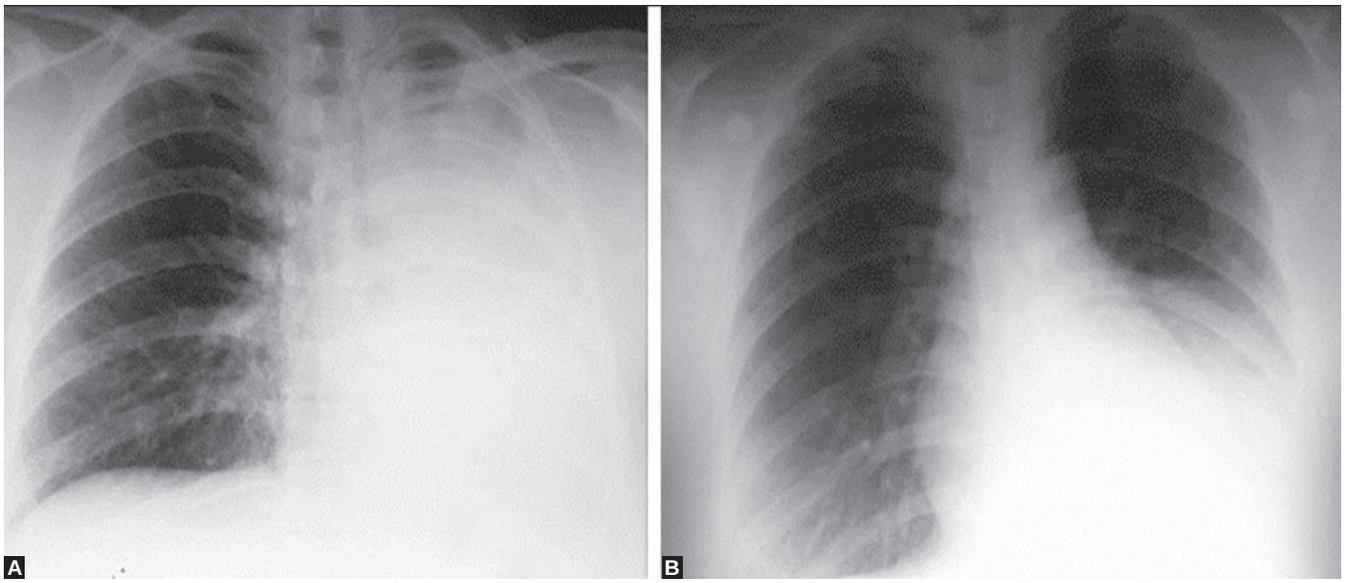


Fig. 44: Septic emboli. Chest X-ray reveals multiple well-defined round and cavitating lesions in both lung fields representing septic emboli



Figs 45A and B: Mucus plug. (A) Chest X-ray reveals dense opacity in left hemithorax with shift of mediastinum to left. In view of the volume loss, dense opacity in left hemithorax bronchoscopy performed; (B) Chest X-ray post scopy reveals clearing of most of the opacity following removal of mucus plug in left main bronchus

Imaging Techniques in the Abdomen

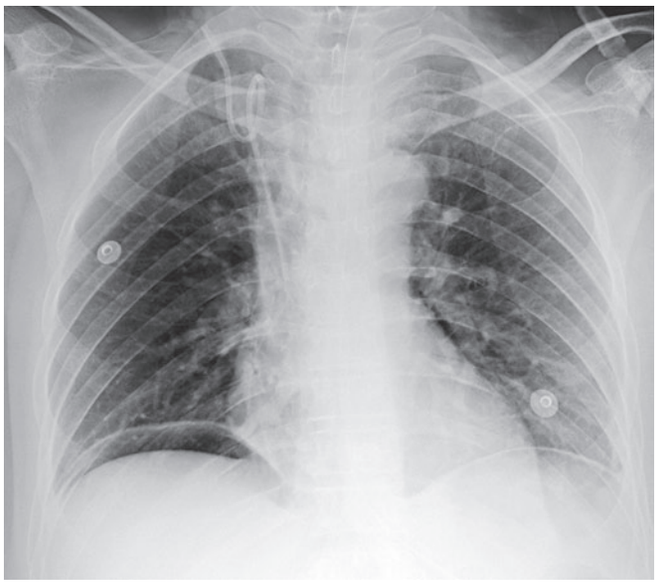


Fig. 1: Pneumoperitoneum: Chest X-ray demonstrates free air under the domes of the diaphragm

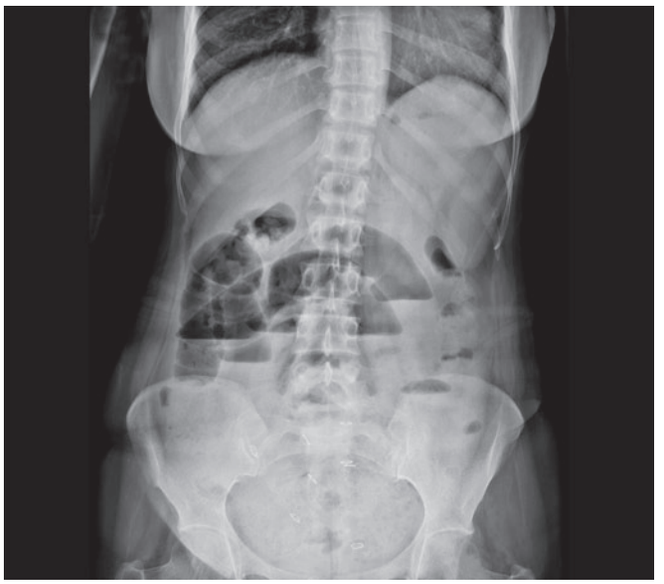
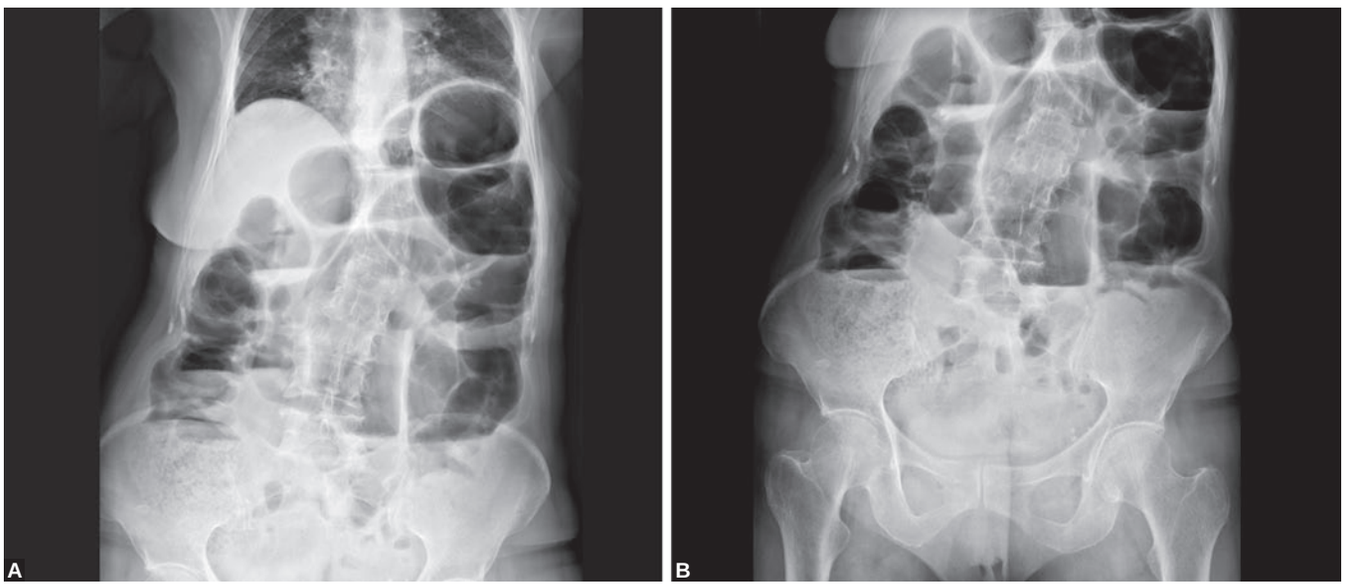


Fig. 2: Small bowel obstruction: Erect abdominal X-ray demonstrates dilated small bowel loops with multiple air-fluid levels



Figs 3A and B: (A and B) Large bowel obstruction: Erect abdominal X-ray demonstrates dilated colonic loops with fluid levels in a patient with colonic obstruction due to sigmoid volvulus

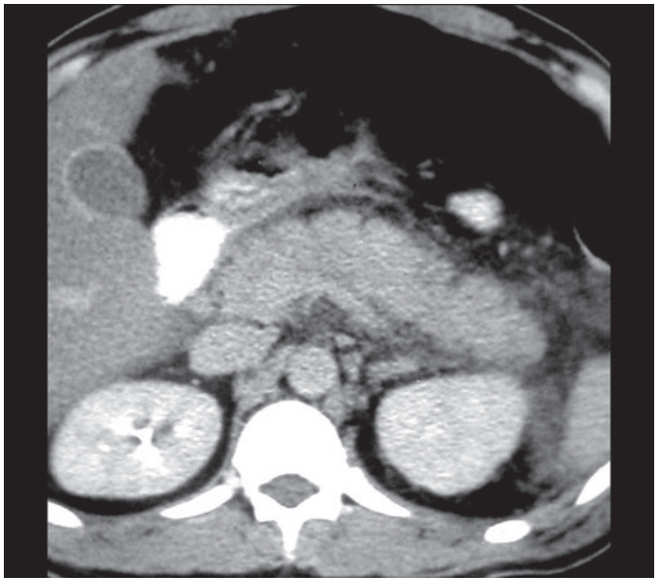


Fig. 4: Acute edematous pancreatitis: Computed tomography (CT) study after administration of contrast reveals an enlarged pancreas with no focal necrosis

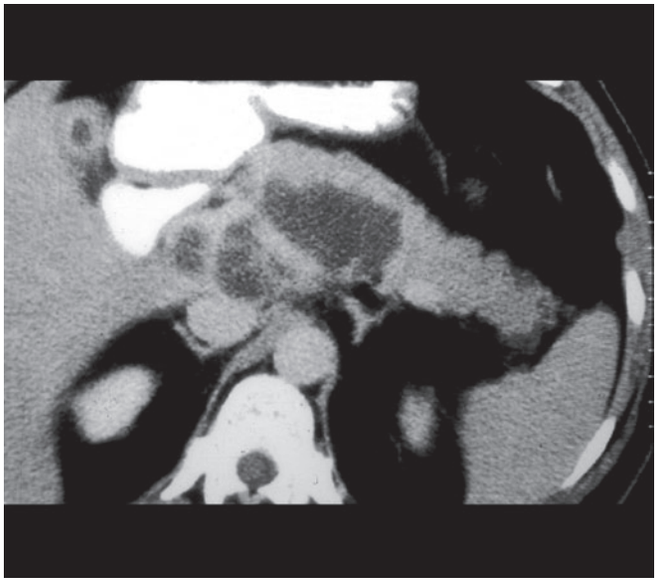


Fig. 5: Necrotizing pancreatitis: Computed tomography (CT) study after contrast reveals focal hypodensities in an enlarged pancreas representing necrotizing pancreatitis

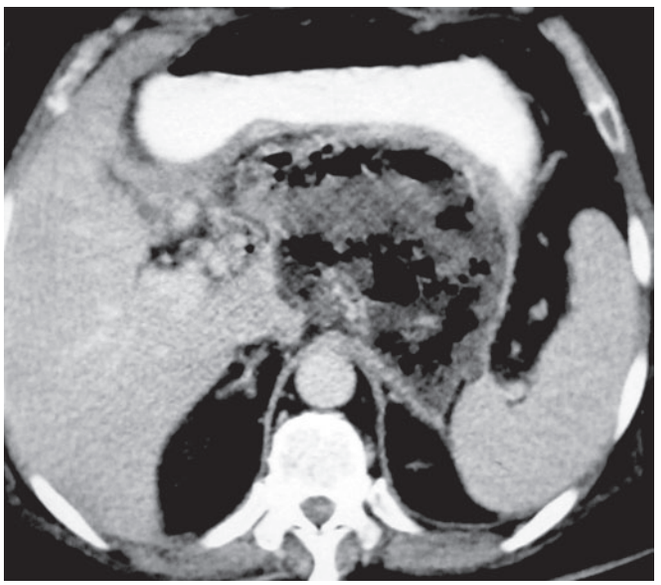


Fig. 6: Pancreatic sepsis: Computed tomography (CT) study after contrast reveals a large collection in the lesser sac with air within, in a case of acute pancreatitis representing pancreatic sepsis

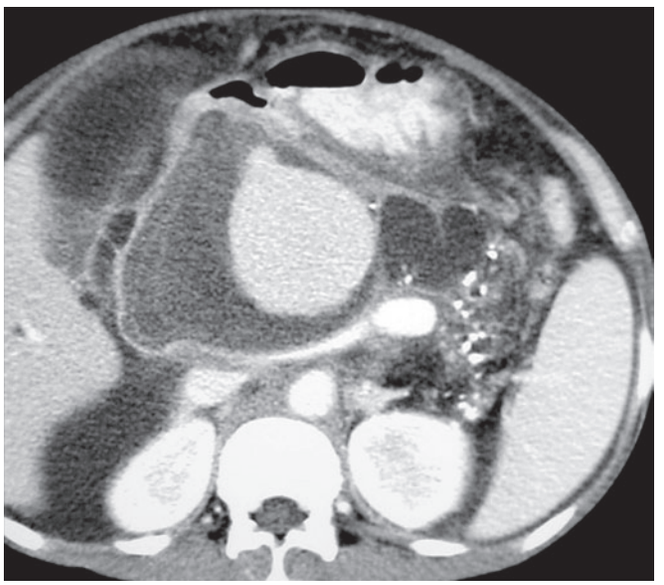


Fig. 7: Pseudoaneurysm following acute pancreatitis: Computed tomography (CT) study after administration of intravenous (IV) contrast demonstrates a large aneurysm with a peripheral thrombus

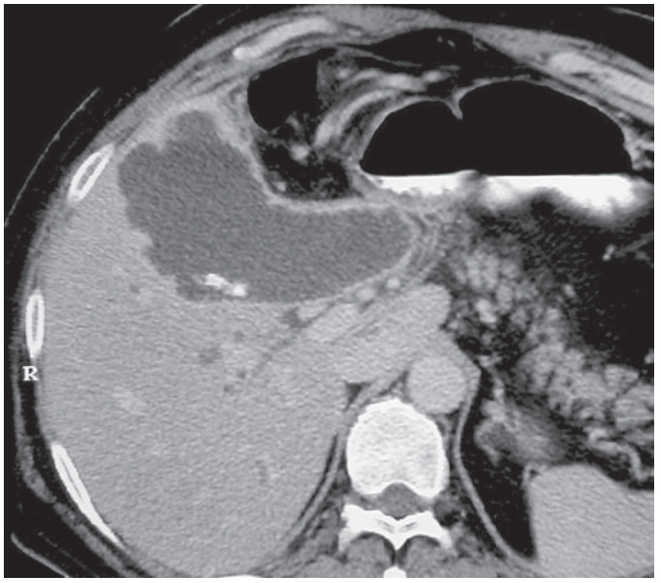


Fig. 8: Acute cholecystitis: Computed tomography (CT) study demonstrates distended gallbladder with an irregular inner surface representing sloughing of mucosa due to gangrenous changes

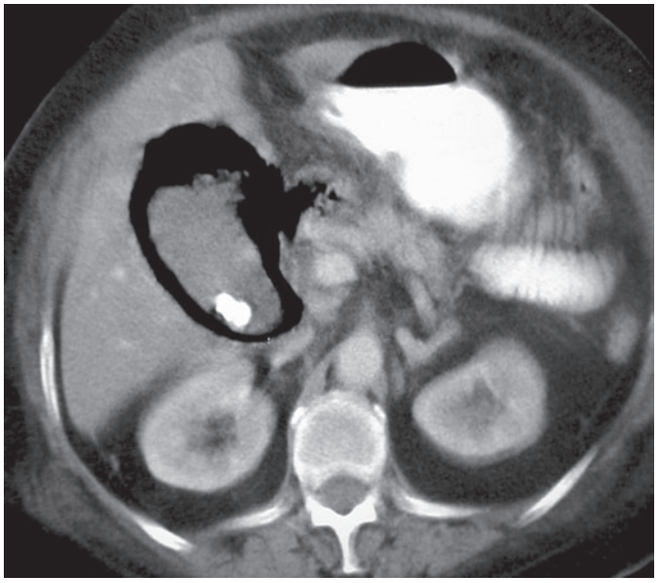


Fig. 9: Emphysematous cholecystitis: Computed tomography (CT) study demonstrates air in gallbladder wall due to emphysematous cholecystitis

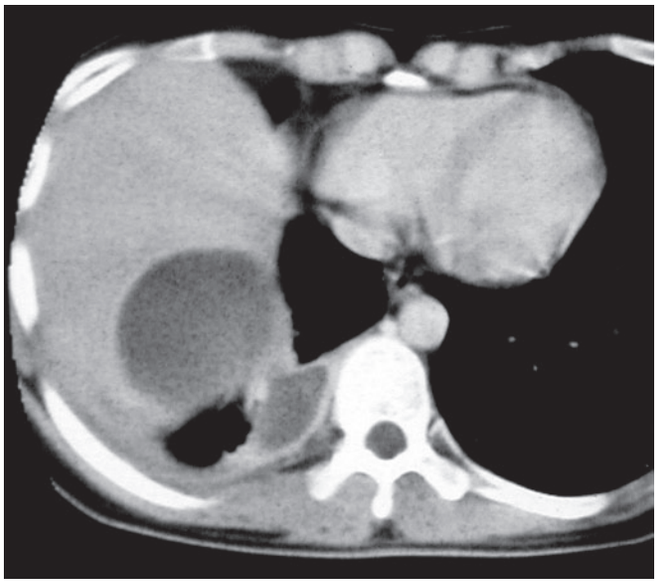


Fig. 10: Ruptured amebic abscess: Computed tomography (CT) demonstrates a well-defined hypodense lesion in the liver with extension into the pleural space

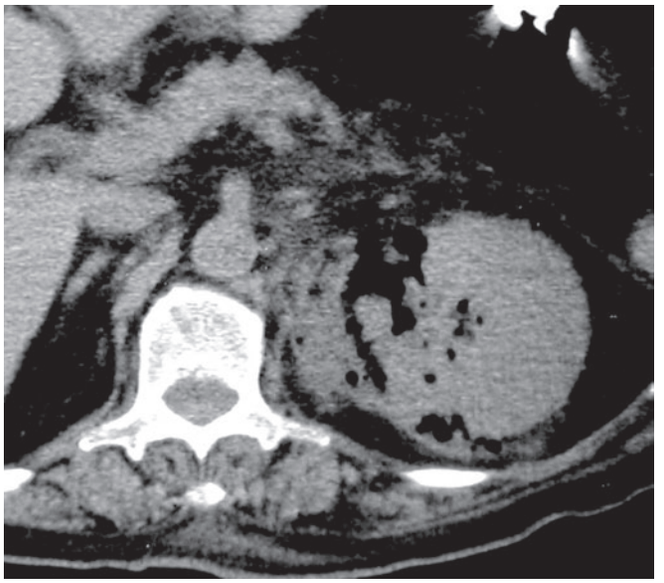


Fig. 11: Emphysematous pyelonephritis: Computed tomography (CT) demonstrates air in the left kidney as a result of emphysematous pyelonephritis

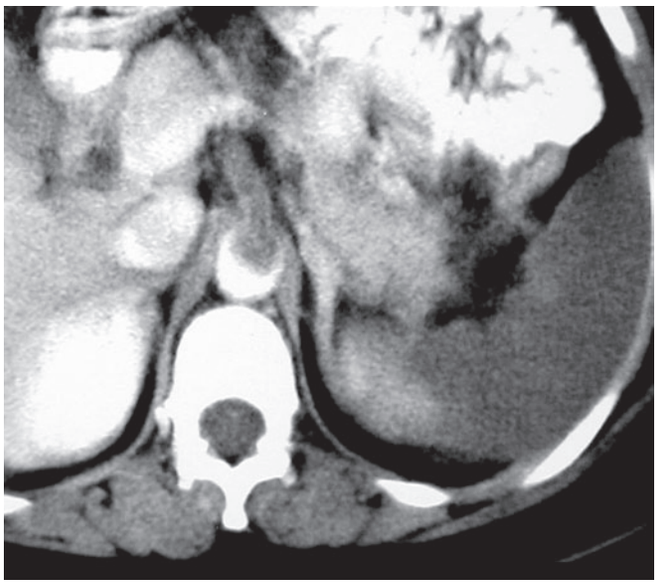


Fig. 12: Splenic infarction: Computed tomography (CT) demonstrates a thrombus in the celiac artery. Note hypodense non-enhancing spleen which is infarcted

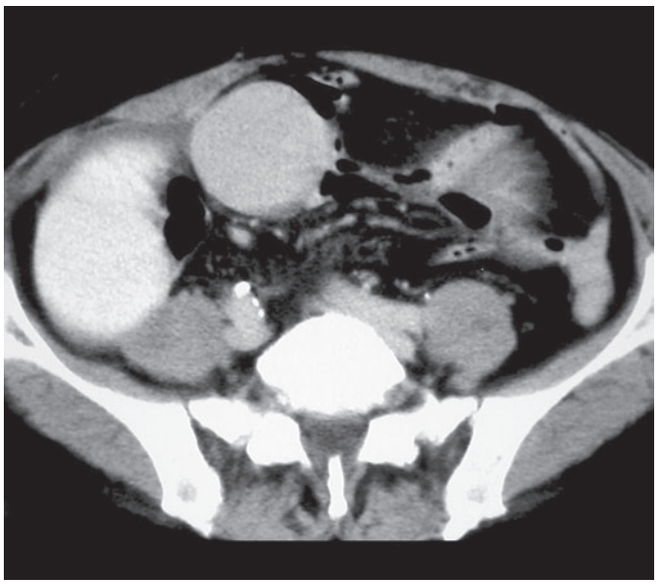
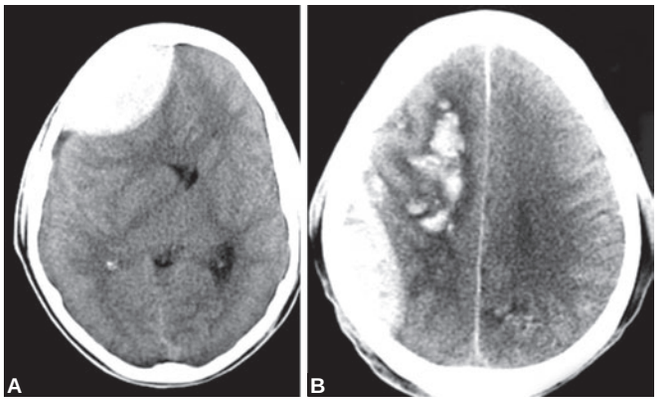
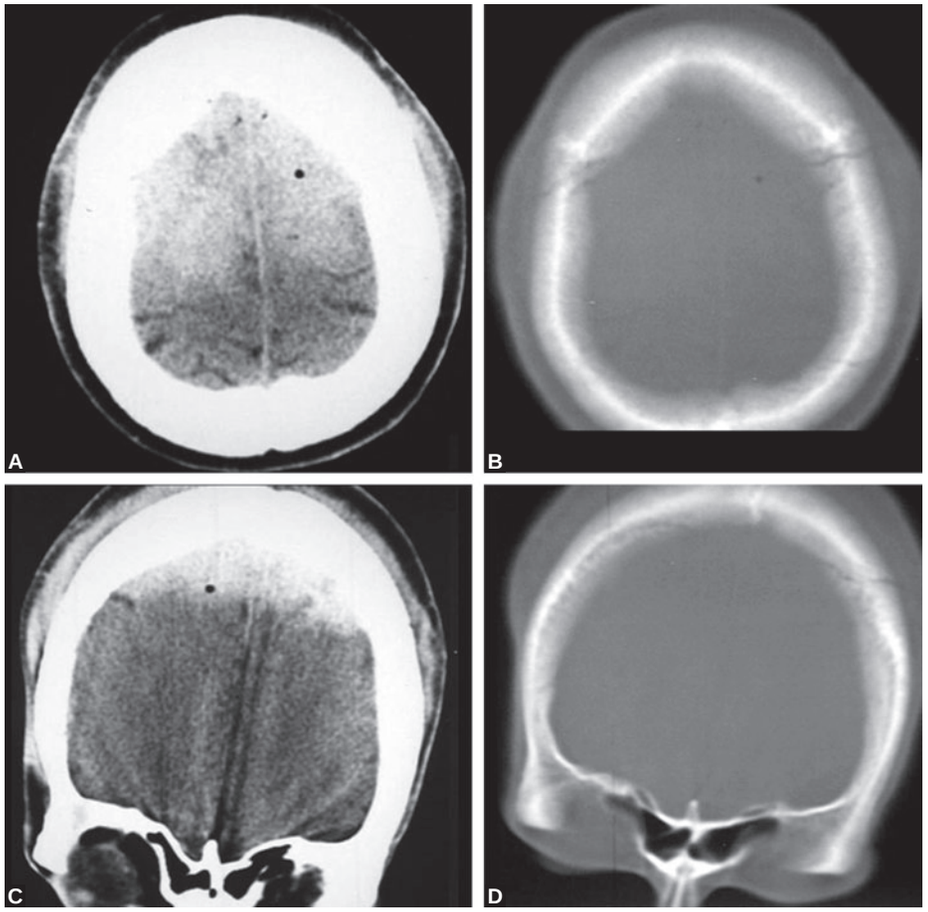


Fig. 13: Small bowel obstruction due to adhesions: Computed tomography (CT) demonstrates dilated small bowel loops, a zone of transition and nondilated loops. There is no mass lesion or obstructing pathology at the zone of transition indicating the obstruction would be due to adhesions or bands



Figs 1A and B: (A and B) Extradural hematoma: Large biconvex extra-axial hyperdensity representing an extradural hematoma



Figs 2A to D: (A to D) Extradural hematoma: Axial and coronal CT demonstrate hyperdensity in the high parietal region in an extra-axial location crossing the midline representing an extradural hematoma

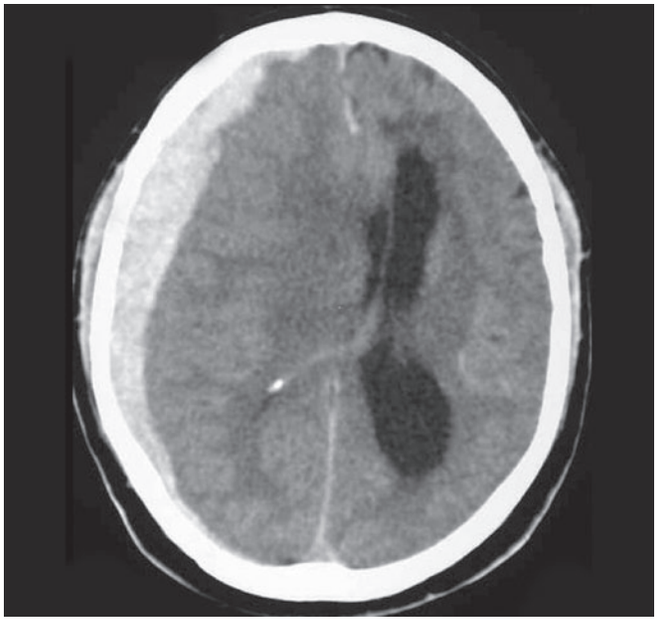
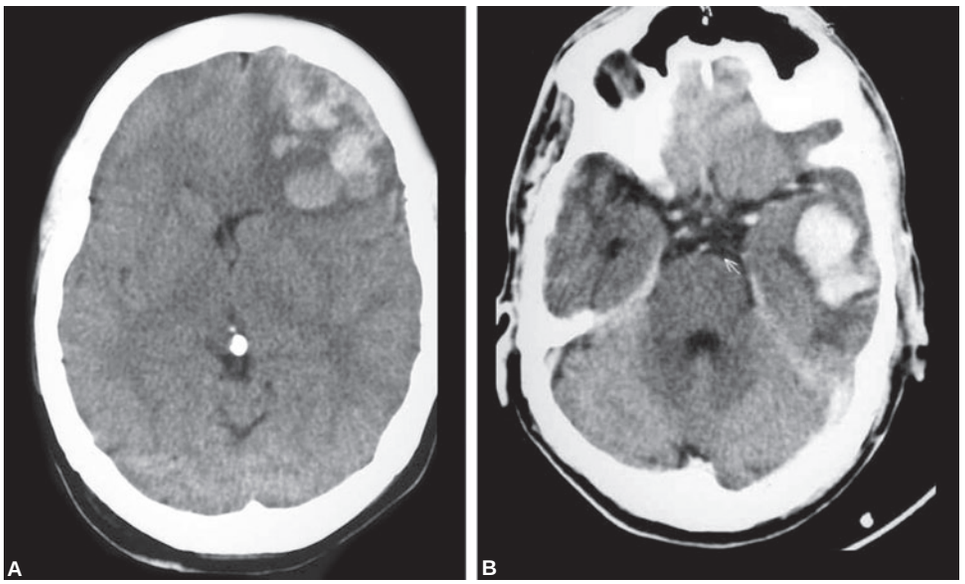


Fig. 3: Acute subdural hematoma: Plain CT brain reveals right concavo-convex hyperdense bleed with compression of the underlying brain parenchyma, there is a shift of the midline structures with consequent dilatation of the left lateral ventricle



Figs 4A and B: (A and B) Hemorrhagic contusions: There are multiple ill-defined hyperdense areas in the left frontal and temporal region causing mass effect on the left lateral ventricle

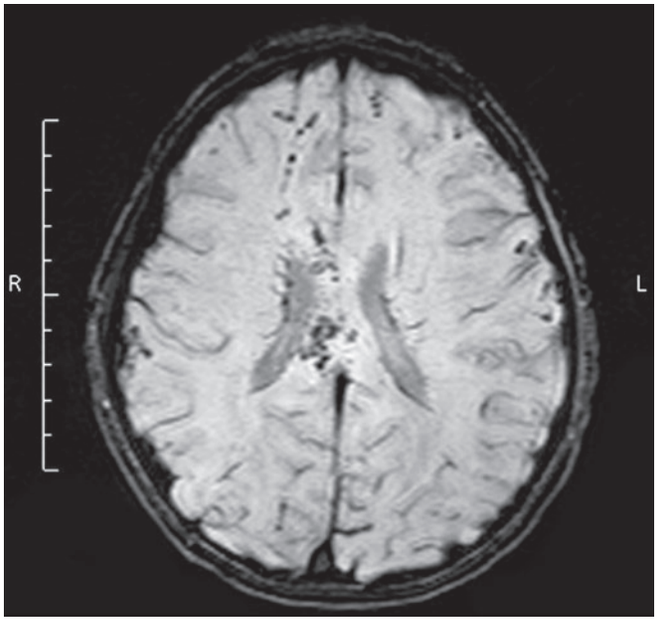


Fig. 5: Diffuse axonal injury: MRI study using susceptibility-weighted imaging (SWI) sequence—demonstrates small petechiae of hemorrhage in the body of the corpus callosum and fronto parietal cortices as a result of shearing injury

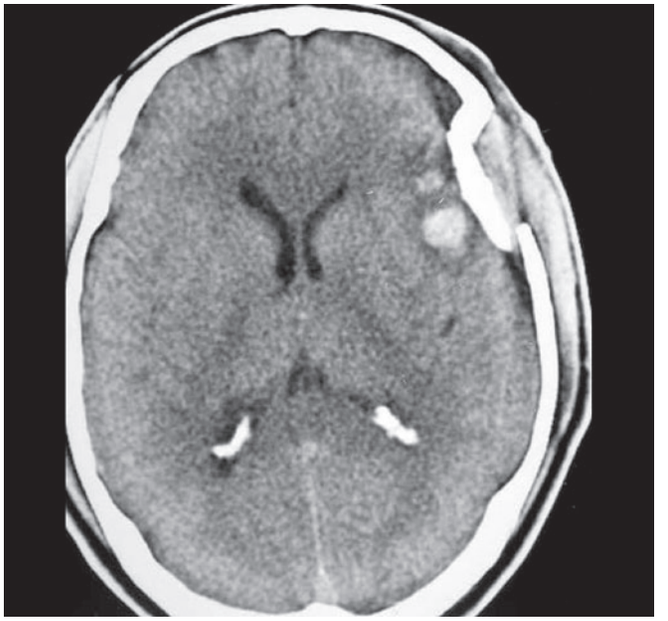
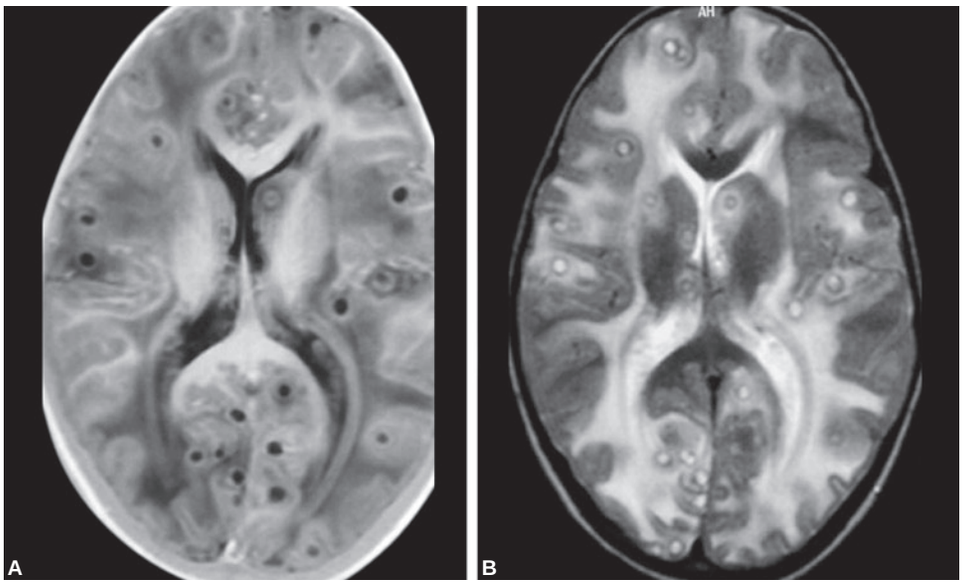
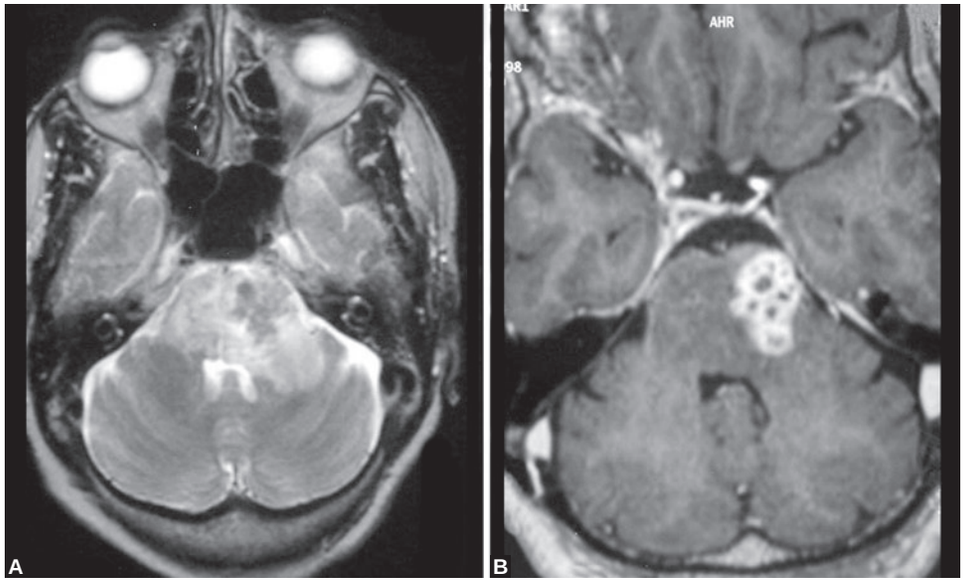


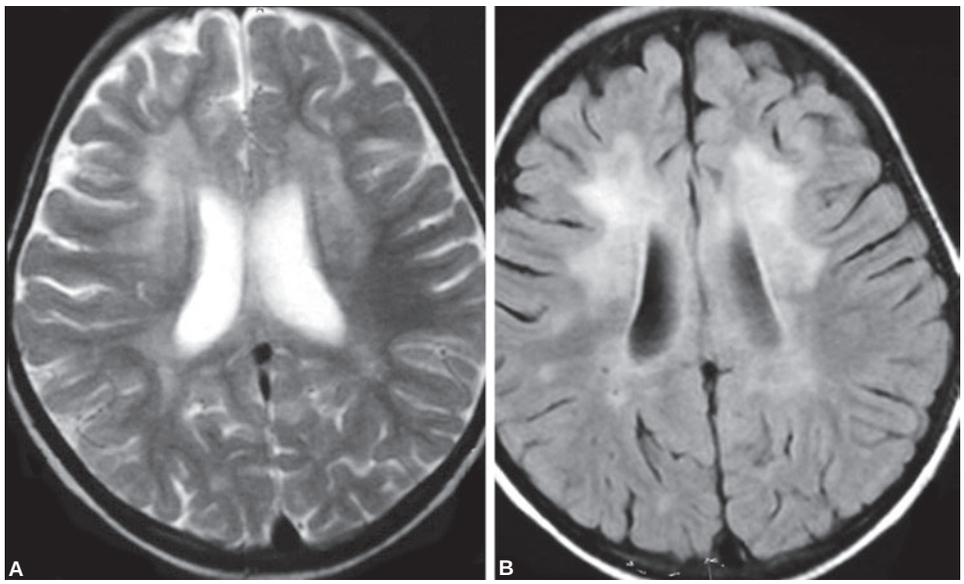
Fig. 6: Depressed fracture with hemorrhagic contusions: Plain CT demonstrates a depressed fracture in the left frontal region with underlying hemorrhagic contusion



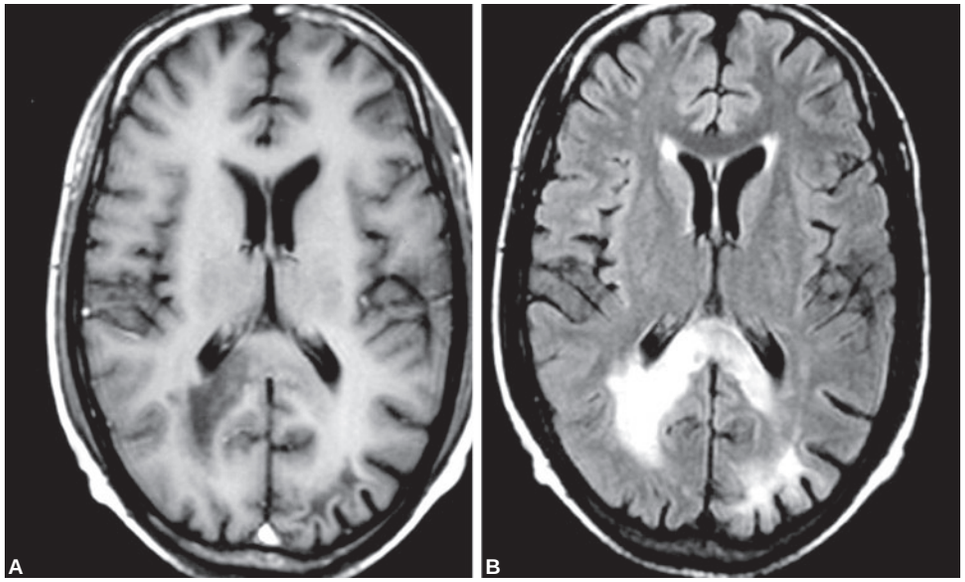
Figs 7A and B: (A and B) Neurocysticercosis: MRI study demonstrates Multiple T1 hypointense and T2 hyperintense well-defined lesions with perifocal edema representing dying cysticerci



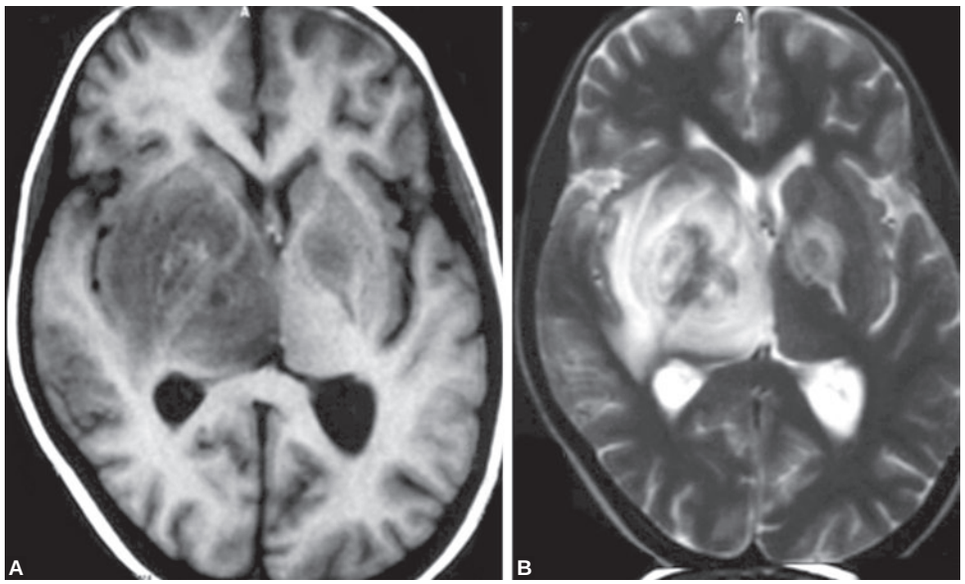
Figs 8A and B: Tuberculomas: (A) Axial T2-weighted image demonstrates conglumerative T2 hypointense lesions in left pons with perifocal edema; (B) Axial post-contrast MRI demonstrates conglumerative ring enhancement



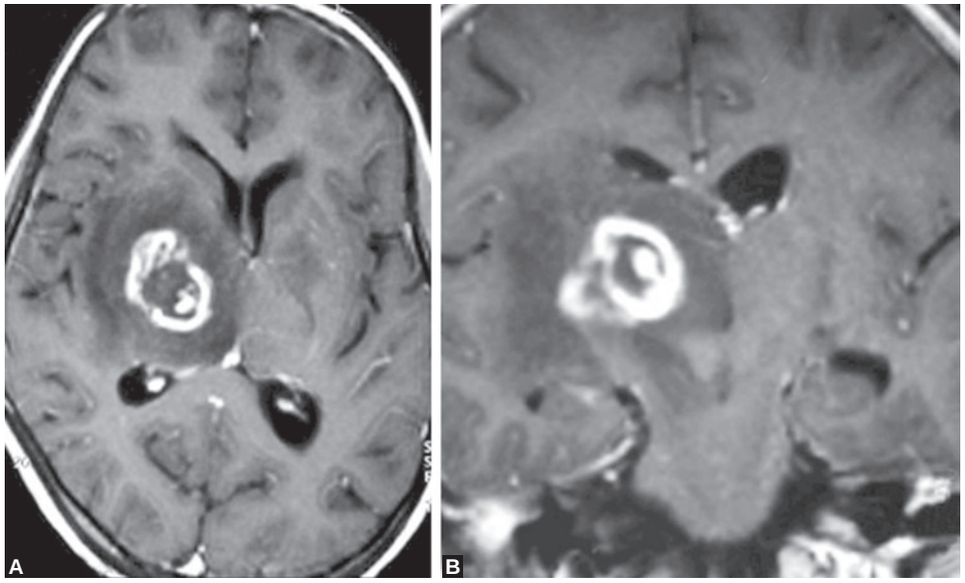
Figs 9A and B: (A and B) HIV encephalitis: Axial T2 and FLAIR images demonstrate hyperintensity periventricular white matter due to HIV encephalitis



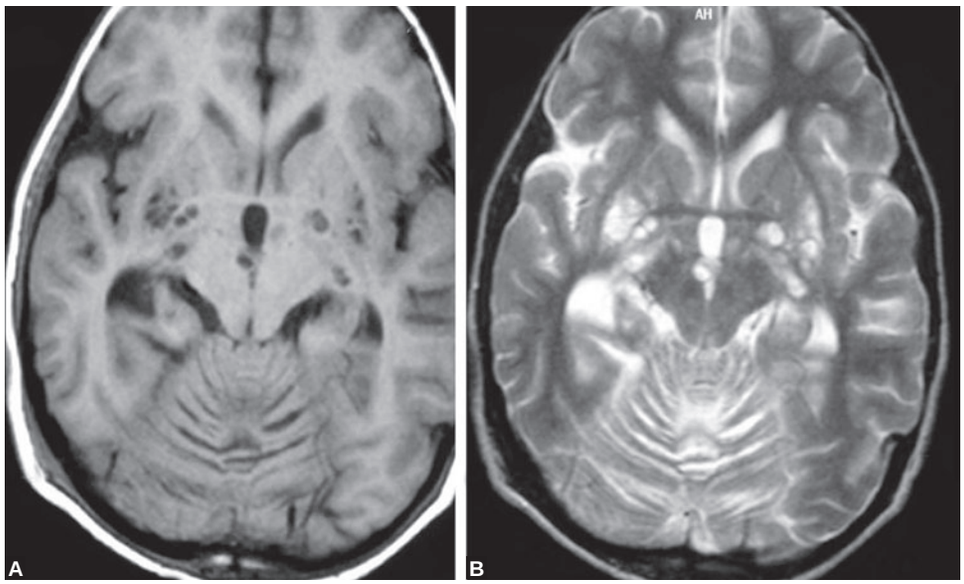
Figs 10A and B: (A and B) PML: T1-weighted image and FLAIR images demonstrate altered signal intensity in the splenium of the corpus callosum with extension to the occipital subcortical white matter



Figs 11A and B: (A and B) Toxoplasmosis: T1- and T2-weighted MRI demonstrates altered signal intensity in both basal ganglia. There are focal T2 hypointense lesions in the basal ganglia with perifocal edema and mass effect



Figs 12A and B: Toxoplasmosis: (A and B) On the post-contrast scans there is peripheral enhancement. The basal ganglia location is characteristic for toxoplasmosis



Figs 13A and B: (A and B) Cryptococcosis: Axial T1- and T2-weighted MRI demonstrates well-defined cerebrospinal fluid (CSF) attenuation areas with no associated perifocal edema in the basal ganglia indicative of gelatinous psuedocysts of cryptococcosis

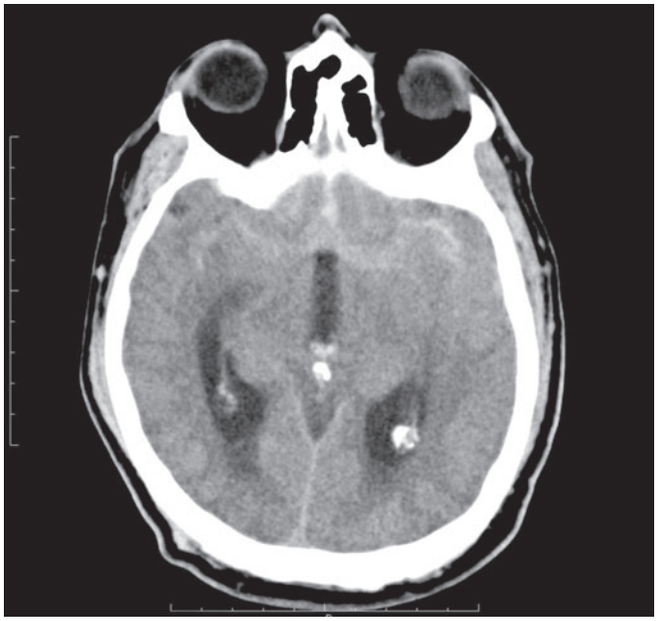


Fig. 14: Subarachnoid hemorrhage: Axial CT demonstrates hyperdensity in subarachnoid space due to subarachnoid hemorrhage

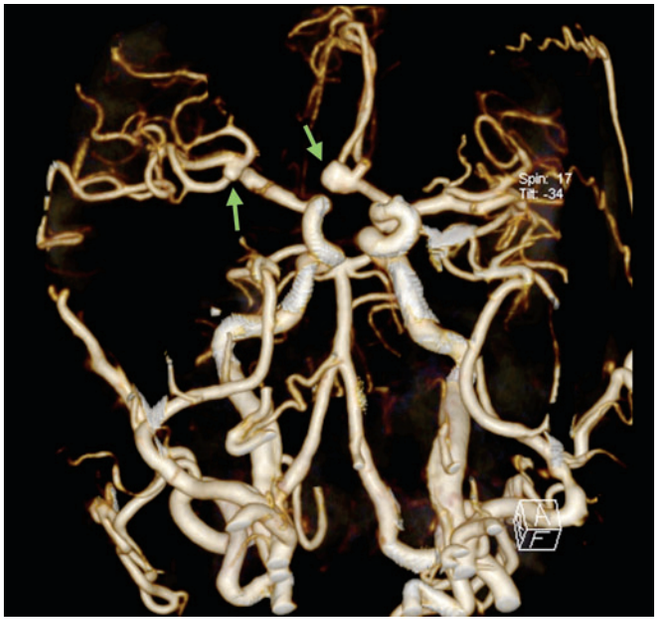


Fig. 15: CT Angio demonstrates anuerysms in relation to anterior communicating artery (ACom) and M2 segment of right middle cerebral artery (MCA)

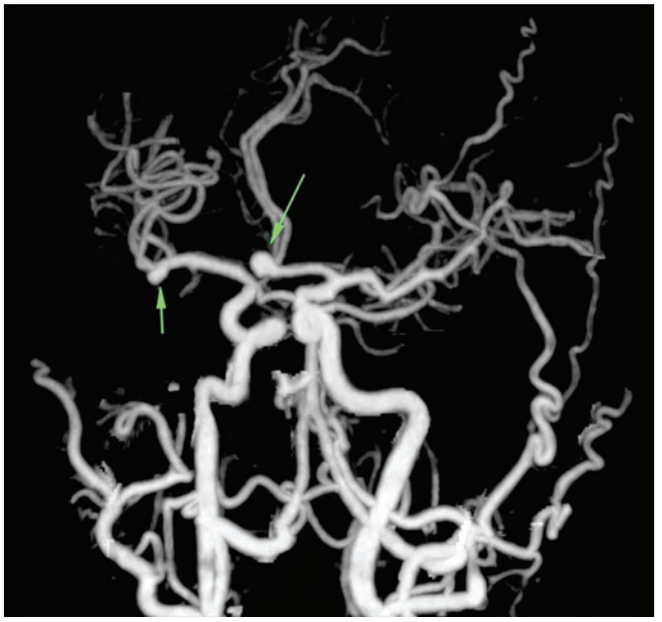


Fig. 16: MRI Angio demonstrates anuerysms in relation to anterior communicating artery (ACom) and M2 segment of right middle cerebral artery (MCA)

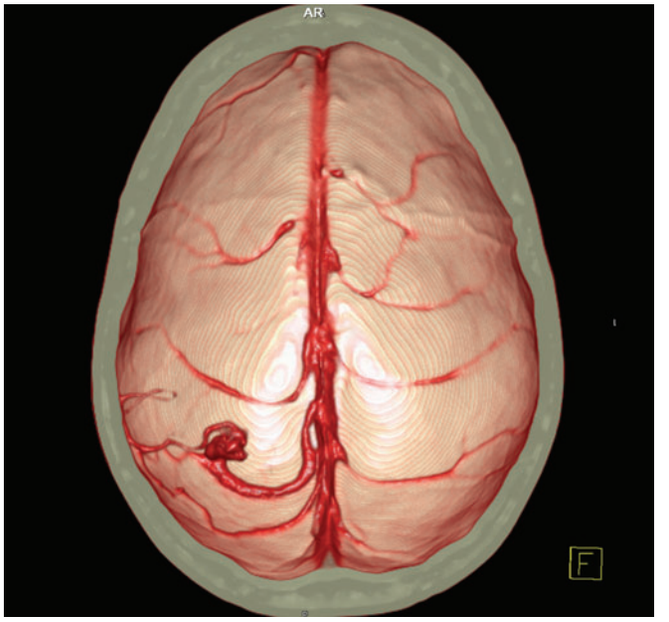


Fig. 17: Arteriovenous malformations (AVM): CT Angio demonstrates an angiomatous malformation in the right parietal region, feeding artery and draining vein are demonstrated

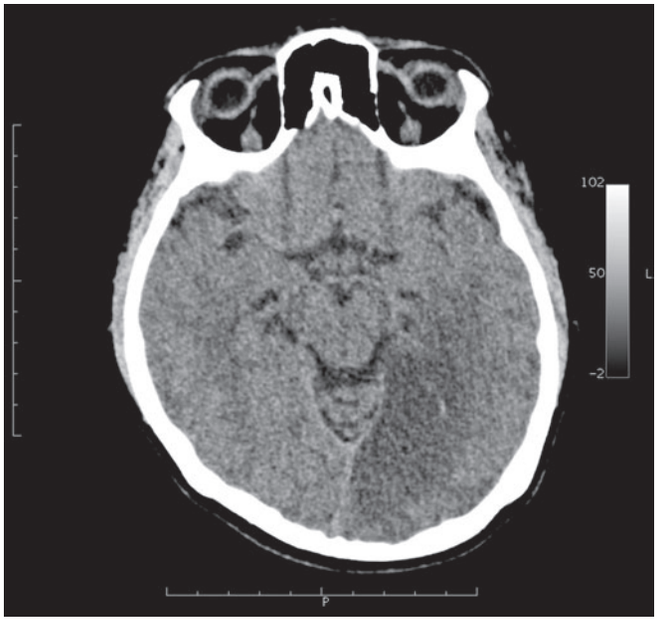
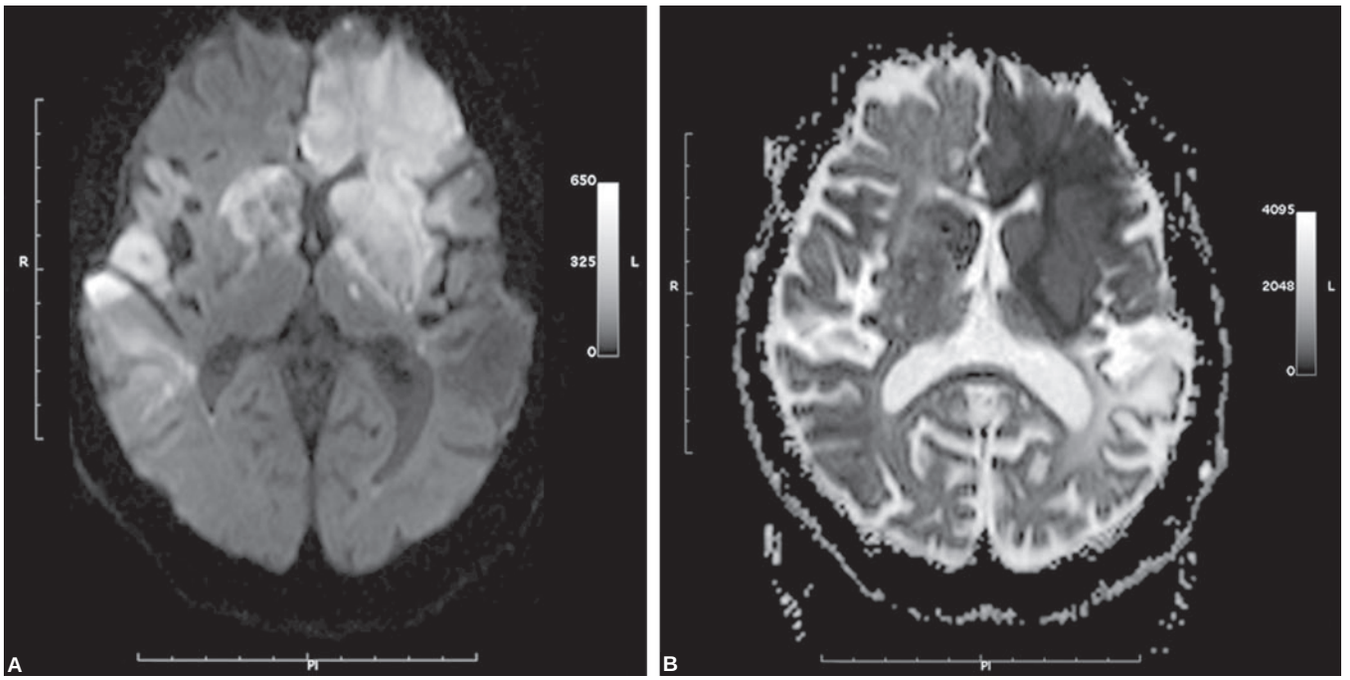


Fig. 18: Acute infarct: CT demonstrates a large hypodensity in the left occipital lobe involving the cortex representing a fresh infarct in the left posterior cerebral artery (PCA) territory



Figs 19A and B: (A and B) Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) images to show a large Lt middle cerebral artery (MCA) territory infarct. With diffusion restriction and ADC drop. Additionally, focal areas of restricted diffusion and ADC drop in the right sylvian cortex and subcortical region

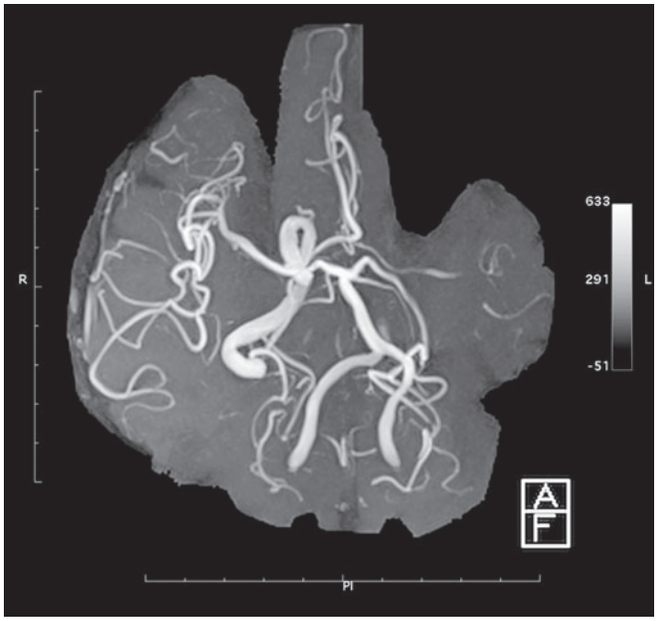
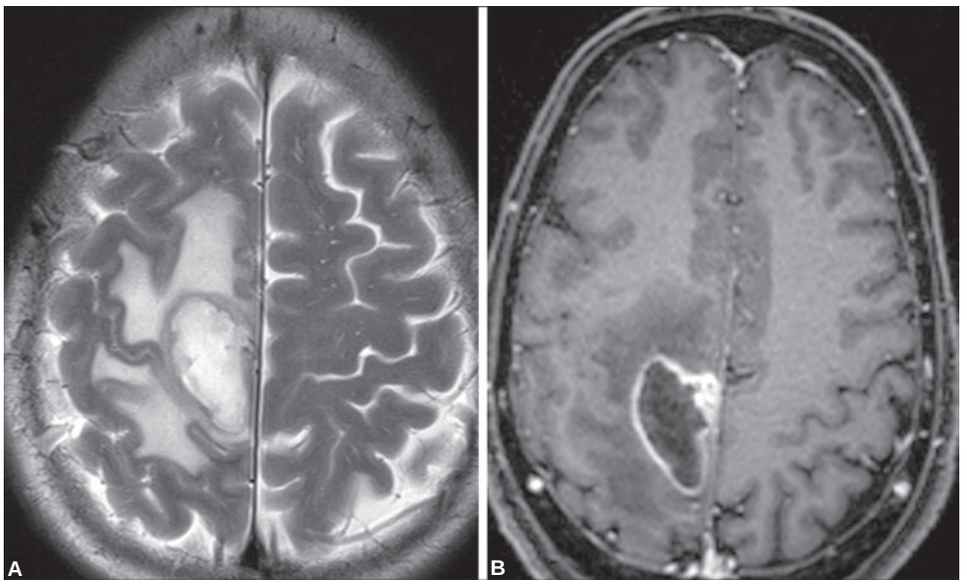
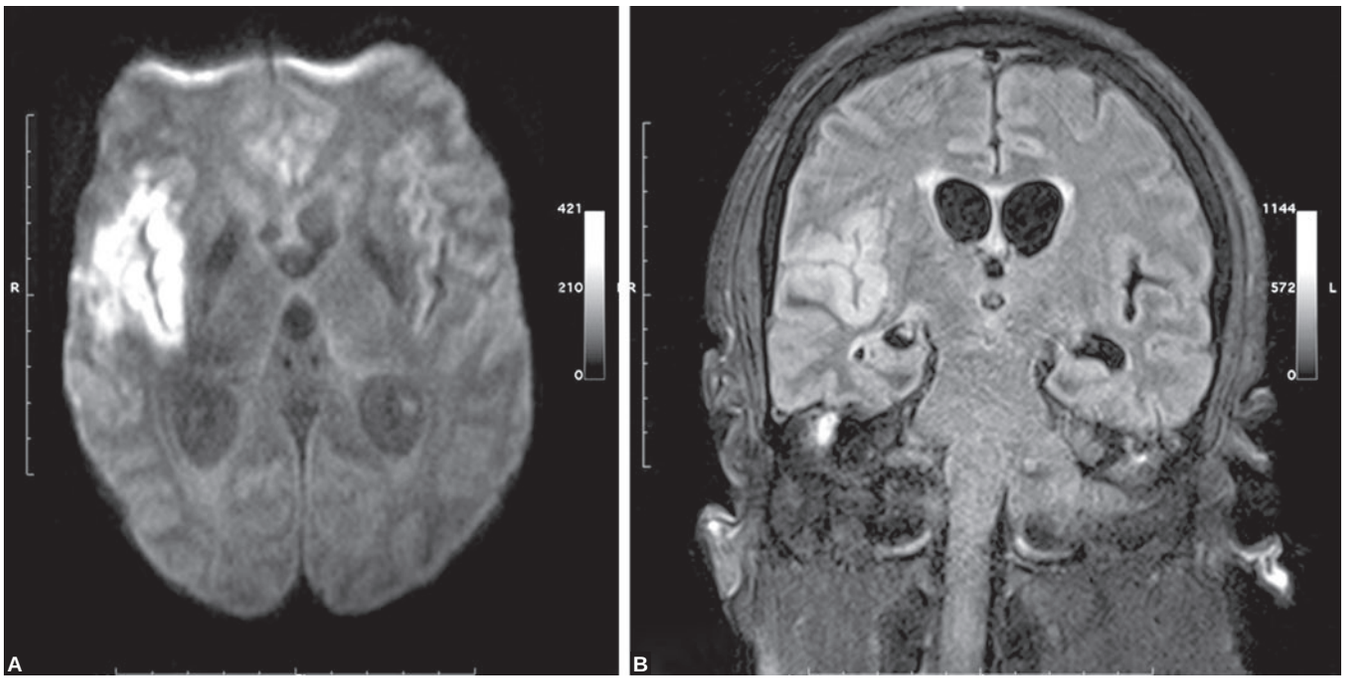


Fig. 20: MR Angio demonstrates total occlusion of left middle cerebral artery



Figs 21A and B: (A and B) Cerebral abscess: Axial T2-weighted image shows an ill-defined hyperintense lesion in the right high parietal region with a T2 hypointense capsule and perifocal edema; (B) Post-contrast MRI demonstrates ring enhancement indicative of a cerebral abscess



Figs 22A and B: Herpes simplex encephalitis: (A and B) Diffusion images demonstrate restricted diffusion in the right perisylvian region. A typical location for herpes simplex encephalitis

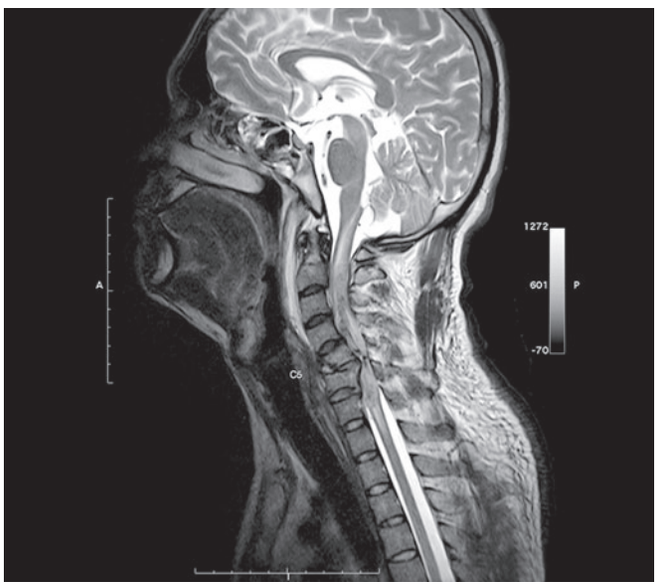
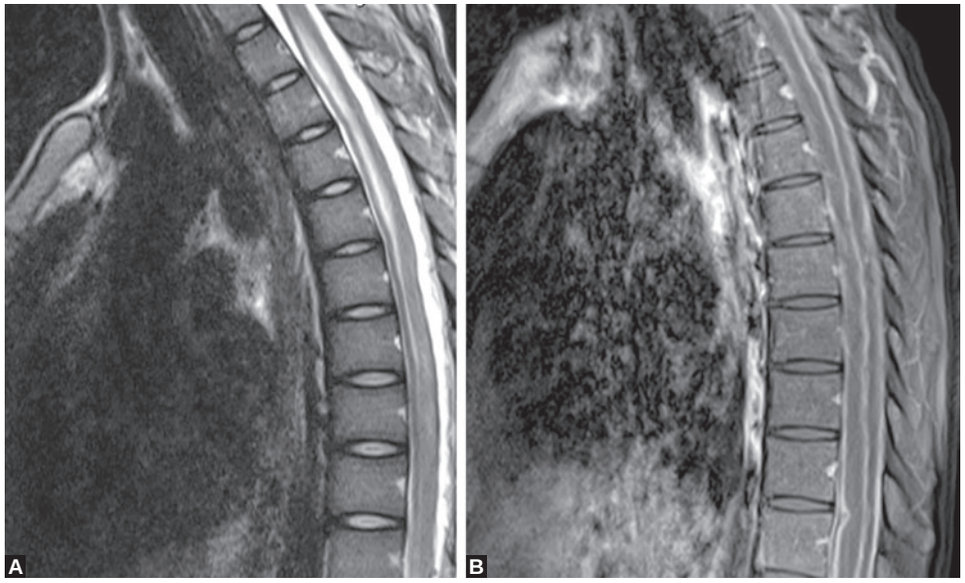


Fig. 23: Cervical trauma: Sagittal MRI demonstrates compression fractures with retro pulsion of c5/c6 vertebral bodies causing significant compression and altered signal intensity in the cervical cord



Figs 24A and B: (A and B) Myelitis: Sagittal T2-weighted image demonstrates altered signal intensity in the dorsal cord, post-contrast MRI demonstrates enhancement along the cord surface and dura. This was of tuberculous etiology

SECTION

6

Clinical Shock Syndromes

- Overview of Shock Syndromes
- Hypovolemic and Hemorrhagic Shock
- Cardiogenic Shock
- Sepsis and Septic Shock
- Cardiac Compressive Shock
- Anaphylactic Shock

CHAPTER 13

Overview of Shock Syndromes

GENERAL CONSIDERATIONS

Shock is a state of acute circulatory failure in which there is reduced tissue perfusion, resulting in tissue hypoxemia, the oxygen supplied to the tissues being inadequate to meet their metabolic requirements. It is a syndrome, a symptom-complex recognized by clinical features many of which are subjective and therefore imprecise. Shock on a close analysis is not a single physiological entity, but a group of life-threatening circulatory syndromes with varying physiological profiles. Though hypotension is a feature of severe shock, the shock syndromes cannot just be equated to hypotension or to a fall in cardiac output (CO) or to accompanying changes in circulatory hemodynamics. It is a major misconception that correction of hypotension and restoration of a normal hemodynamic profile is the be-all and end-all in the management of shock. Shoemaker[1] evaluated the significance of restored hemodynamic parameters in a series of critically ill survivors and non-survivors with shock. With therapy, mean arterial blood pressure (ABP mean), heart rate (HR), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) and CO were restored to normal in 76% of non-survivors who still went on to die. Obviously, though restoring the hemodynamic profile in shock to as near normal as possible is important, it is simply not enough. Thus, a restored hemodynamic profile in shock may for various reasons be associated with an impaired microcirculation to various organs leading to persistent hypoperfusion and hypoxia to tissue cells. There is more to the management of shock than the mere restoration of circulatory hemodynamics.

What needs to be stressed is the concept that every form of severe shock is characterized by inadequate tissue oxygenation. Marino[2] expresses this succinctly when he points out that shock is buried in the tissues and that an approach that helps assess tissue oxygenation should be central to its management. What complicates matters is that in shock, different tissues may have different or varying needs for oxygen. To accurately evaluate the effects of restoration of the circulation on the oxygenation of tissues within different organ systems, particularly in critically ill individuals, may therefore seem an impossibly difficult task. How does one ensure that the oxygen uptake by tissues ($\dot{V}O_2$) is matched to metabolic needs? The balance between $\dot{V}O_2$ on the one hand, and the metabolic rate or needs on the other, can be indirectly determined by measuring the lactate levels in arterial blood.[2] A blood lactate level well above normal, points to anaerobic tissue metabolism, which again suggests that tissue requirements for oxygen are not being met.

MICROCIRCULATORY MITOCHONDRIAL DYSFUNCTION SYNDROME[3]

In this condition, the hemodynamic profile of shock may through treatment return to normal, yet tissue hypoxia can persist because of an abnormal capillary microcirculation. This may well be associated with cell mitochondrial dysfunction. Though mitochondrial dysfunction may be the result of poor tissue perfusion because of microcirculatory dysfunction, it may occur independently of the latter. This syndrome has been studied particularly in patients with septic shock. It should be suspected when a rise in the serum lactate persists in spite of a normal hemodynamic profile and a normal oxygen delivery (DO_2). It is discussed further in the Chapter Sepsis and Septic Shock.

One other important manifestation of circulatory shock (besides hypoperfusion, hypoxia detected by increased

lactate levels in blood) is the inducement of the systemic inflammatory response syndrome (SIRS).[4] Hypoperfusion and resuscitation (ischemia—reperfusion) can initiate SIRS which then literally feeds upon itself through various mechanisms touched upon in the Chapter Sepsis and Septic Shock. The inflammatory component may be less marked (as in quickly resuscitated hypovolemic or cardiogenic shock), large (as in septic shock) or intermediate (as in many patients with traumatic shock). This inflammatory component of shock (particularly in patients with septic shock and shock due to trauma) often determines the final outcome as it sets into motion a vicious downward spiral that can lead to progressive multiple organ dysfunction, failure and death.

Survival in shock is determined by the ability of the circulation to match oxygen supply to tissue needs for oxygen. It is important that this is achieved before permanent tissue damage has occurred. Therapy, which is adequate but delayed, may be ineffective, for there comes in the natural history of shock, a point beyond which there is no return.

CLASSIFICATION OF SHOCK

Shock can be due to a number of etiological factors. Basic forms of shock include hypovolemic shock, cardiogenic shock, obstructive shock and vasogenic or distributive shock. The different types of shock have been classified in Box 1. The basic hemodynamic profiles of each of these shock syndromes are briefly described below.

Hypovolemic Shock

Shock due to hypovolemia is characterized by a loss in circulatory volume which results in a decreased venous return, a decreased filling of the cardiac chambers, and hence a decreased CO which leads to an increase in the systemic vascular resistance (SVR). The hemodynamic profile on monitoring of flow pressure variables shows a low CVP, a low PCWP, a low CO and cardiac index (CI), and a high SVR. The arterial blood pressure may be normal or low.

Cardiogenic Shock

Cardiogenic shock is primarily dependent on poor pump function. Cardiogenic shock due to acute catastrophic failure of left ventricular pump function is characterized by a high PCWP, a low CO and CI, and generally a high SVR. When overall pump function of both right and left ventricles fails, the hemodynamic profile is more complex (see Chapter Cardiogenic Shock).

Obstructive Shock

Obstructive shock is usually due to acute pulmonary embolism, cardiac tamponade and tension pneumothorax. The filling pressures are raised due to outflow obstruction, impaired ventricular filling; the blood pressure and cardiac output are low and the systemic vascular resistance increased. The hemodynamic profile may closely resemble that observed in cardiogenic shock.

Box 1: Classification of shock

- Hypovolemic and hemorrhagic
- Cardiogenic—
  - Acute myocardial infarction
  - Cardiomyopathy
  - Cardiac arrhythmias
  - Mechanical causes, e.g. valvular disease, outflow tract obstruction, ruptured ventricular septum or chordae tendinae
- Obstructive—
  - Pulmonary embolism
  - Cardiac tamponade
  - Tension pneumothorax
- Distributive or vasogenic—
  - Septic shock, toxic shock syndrome
  - Anaphylactic
  - Neurogenic

Vasogenic or Distributive Shock

This shock syndrome occurs with a number of etiological factors and is characterized by a poor vascular tone in the peripheral circulation (low SVR). There is also a maldistribution of blood flow to organs within the body. The CO varies but is usually raised. A common hemodynamic profile is a low or normal PCWP, a high CO, a low arterial blood pressure, and a low SVR. Vasogenic shock is typified by septic shock and the toxic shock syndrome. It is also observed in traumatic shock, neurogenic shock following spinal cord trauma, in postoperative shock, shock in pancreatitis and in anaphylactic shock. Septic shock, toxic shock syndrome and anaphylactic shock have been described in subsequent chapters. The hemodynamic profiles in the various categories of shock are given in Table 1.

Though the above categories of shock and their hemodynamic profiles are easily understood and generally accepted for teaching purposes, in actual practice, problems in assessment and management of shock syndromes are often complex and difficult. For example, the features of hypovolemia, myocardial dysfunction and sepsis may all be present in the same individual. Similarly, hypovolemia may be present in some patients with cardiogenic shock. Patients in

Table 1: Hemodynamic profiles in the various categories of shock

	MAP	PAWP	CO	SVR
Hypovolemic, hemorrhagic shock	↓	↓	↓	↑
Cardiogenic shock	↓	↑	↓	↑
Obstructive pulmonary embolism, pericardial tamponade, tension pneumothorax	↓	↔↑	↓	↑
Distributive, vasogenic shock, septic shock, adrenal insufficiency, anaphylaxis, neurogenic	↓	↔↓	↔↑	↓

Abbreviations: CO, cardiac output; MAP, mean arterial pressure; PAWP, pulmonary arterial wedge pressure; SVR, systemic vascular resistance.

cardiogenic shock following myocardial infarction and cardiac surgery may develop vasodilation due to active mediator release and thereby also show features of distributive shock. Acute circulatory failure triggers a chain of compensatory responses, chiefly mediated by neurohormonal mechanisms. These compensatory responses alter the hemodynamic profile induced by the initial insult to the circulation. Compensatory features in shock, particularly changes in SVR vary from patient to patient. Old age, neuropathies and diabetes mellitus are some important background factors that can blunt the systemic vascular response and other compensatory responses. Then again, various therapeutic modalities instituted in the management of shock can alter the hemodynamics of shock and its hemodynamic profile, and this alteration may last for only a short period of time. Finally, not only compensatory mechanisms but also decompensation within the circulatory system can further produce varying hemodynamic profiles in different shock syndromes.

Hence, the assumption that each cause of shock necessarily has a characteristic profile, and that therapeutic principles in management are dependent on analyzing one single profile at any one point in time, is simplistic and beset with difficulties. Various permutations and combinations of the above basic hemodynamic profiles can lead to a number of possible patterns. However, familiarity with the basic profiles described above helps the intensivist analyze the hemodynamic changes that can occur in shock syndromes, and aids in management.

MONITORING TISSUE HYPOXEMIA AND PERFUSION FAILURE

The restoration of a normal blood pressure, normal CO and vascular resistance correlates poorly with survival in critically ill patients, particularly in septic shock or shock related to trauma.

This observation has led to the monitoring of indices of tissue oxygen metabolism as markers of tissue perfusion. Newer studies to observe microvascular blood flow in regional vascular beds have also been devised.

Lactate Concentration in Arterial Blood

An increase in serum lactate levels (normal <2 mmoL/L) denotes anaerobic tissue metabolism and tissue hypoxia. An increased lactate level has a serious prognostic significance; a persistence of this increase in spite of resuscitative efforts carries an even worse prognosis. In patients with septic shock, increased lactate levels may be also related to factors other than hypoperfusion—these include decreased hepatic clearance of lactate, increased muscle ATPase activity, decreased pyruvate dehydrogenase activity and cell mitochondrial dysfunction.

Base Deficit

Elevation of the base deficit is an important marker of tissue hypoxemia and acidosis. The normal range of base deficit is –2 to +2 mmoL/L. Increase in base deficit may be mild (–2 to –8 mmoL/L), moderate (–6 to –14 mmoL/L), or severe (< –15 mmoL/L). Magnitude of the base deficit has been shown to correlate with the extent of blood loss in hemorrhagic shock, and a correction of the base deficit within hours of resuscitation carries a favorable prognosis.[2]

Measurement of Mixed Venous Oxygen Saturation

The mixed venous oxygen saturation ($S\dot{v}O_2$) is measured from blood taken from the pulmonary artery via a pulmonary artery catheter and is an index of overall global tissue oxygenation. Increased oxygen extraction from blood perfusing tissues is an important mechanism to maintain oxygen consumption ($\dot{V}O_2$). Hence, a decrease in $S\dot{v}O_2$ is a marker of compromised tissue perfusion. This is particularly so in both hypovolemic and cardiogenic shock. In the latter, a falling $S\dot{v}O_2$ denotes a worsening tissue perfusion due to a falling CO. This relation does not necessarily hold in septic shock and in other conditions where the relation between $S\dot{v}O_2$ and tissue oxygenation is altered by maldistribution of blood flow. In such circumstances, the $S\dot{v}O_2$ may be normal or even increased in spite of tissue hypoxia and anaerobic metabolism. In summary, though a low $S\dot{v}O_2$ is indicative of tissue hypoxemia, a normal or high $S\dot{v}O_2$ does not exclude tissue hypoperfusion.

Measurement of Central Venous Oxygen Saturation ($ScvO_2$)

Measurement of central venous oxygen saturation ($ScvO_2$) through a central venous catheter in the superior vena cava is now increasingly being used as a substitute of $S\dot{v}O_2$. The $ScvO_2$ in critically ill patients is generally 5% higher than the $S\dot{v}O_2$. This correlation is however not always consistent. The advantage of measuring $ScvO_2$ as a substitute for $S\dot{v}O_2$ is that it obviates the need for invasive monitoring through a pulmonary artery catheter.

Oxygen Delivery, Oxygen Consumption Measurements[5]

Oxygen delivery (DO_2) and $\dot{V}O_2$ are global markers for tissue oxygen metabolism.

$$\text{Oxygen consumption } \dot{V}O_2 = Q_T \times CaO_2 - CvO_2$$

where CaO_2 and CvO_2 equal oxygen content in arterial and venous blood respectively and Q_T is the cardiac output.

Oxygen delivery is calculated from CO, Hb and oxygen saturation and is a measure of total oxygen delivered to the tissues.

A reduced DO_2 portends danger. A reduced $\dot{V}O_2$ even in the presence of a normal or increased DO_2 can, if uncorrected, lead to tissue hypoxia. Ordinarily, tissues extract 25% of the oxygen from the blood perfusing them. When DO_2 falls or if metabolic requirements of tissues increase, more oxygen is extracted from the blood perfusing the tissues. This is a

compensatory mechanism that allows the tissues to meet their oxygen demands. If however the oxygen extracted from the blood by the tissues is more than 50% tissue hypoxemia results. Thus, DO_2 and $\dot{V}O_2$ are good markers that help the clinician gauge tissue oxygenation.

End-Tidal CO_2 and Tissue CO_2 Measurements

End-tidal CO_2 and tissue CO_2 measurements are chiefly useful in monitoring cardiopulmonary resuscitation following cardiac arrest. Cardiac arrest leads to absence of blood supply to the lungs, with a sharp fall in CO_2 excretion and therefore a fall in end-tidal CO_2, which approaches zero. The end-tidal CO_2 increases with successful resuscitation and is useful as a marker for the adequacy of resuscitative efforts.

Measures to Estimate Regional Perfusion

Many efforts have been made to use measurements of regional or local perfusion as markers for global perfusion. These include measurements of subcutaneous oxygen tension and transcutaneous oxygen tension. Gastric tonometry and more recently sublingual tonometry have been used to assess CO_2 excess in the vascular beds, and equate this excess as a marker for global hypoperfusion. There are practical difficulties in the above measurements and it is doubtful if they significantly add in the management of the shock syndromes or improve their outcome.

Assessment of Microvascular Blood Flow[6,7]

- Use of near infrared spectroscopy (NIRS) to assess level of oxygenated Hb in the skeletal muscle. The actual value and the response of tissue Hb saturation to reactive hyperthermia are believed to predict survival.[6]
- Orthogonal polarization spectral (OPS) imaging and sidestream dark-field (SDF) imaging have been used to directly visualize microcirculatory flow. A decrease in the microcirculatory flow was noted to correlate with decreased survival rates in septic and cardiogenic shock.[7] Hypoperfusion was seen to persist even after resuscitation had restored a normal hemodynamic profile. It is to be determined whether therapeutic measures directed toward improvement of microcirculation observed by the above techniques will alter the outcome in shock syndromes.

AN OVERVIEW OF MANAGEMENT STRATEGIES IN THE SHOCK SYNDROMES (BOX 2)

The principles of management are as follows—

Treat the Cause Whenever Possible

In hemorrhagic shock, it is important to arrest the source of bleeding in so far as this is possible. Sepsis should be managed by draining local pockets of infection surgically, ensuring that the source of sepsis is eradicated, and by the very early use of appropriate antibiotics. Shock due to pulmonary embolism may warrant thrombolytic therapy. Traumatic shock, shock in an adrenal crisis and in anaphylaxis need appropriate specific therapy outlined in other chapters of this book.

Box 2: Overview of management strategies in the shock syndromes

1. Treat the cause whenever possible
2. Interpret and manage hemodynamic abnormality—
   a. Low CVP and PCWP, hypotension—
      » Volume load to raise CVP >10 mm Hg and PACP to 15–18 mm Hg
      » Use vasopressors or dopamine only if hypotension persists after adequate volume load
   b. Low CO, hypotension, and a normal SVR—
      » If the PCWP is low or normal, it should be pushed to the upper limit or even above normal by a suitable volume load, before starting vasopressor support. Inotropic support may also be necessary
      » If the PCWP is in the upper limit of normal, use vasopressor support. Inotropic support may also be necessary
   c. Low CO, hypotension, and a raised SVR—
      » Volume load to upper limit of filling pressures; if hypotension persists use inotropic support
      » If SVR remains high in spite of adequate volume load, lower SVR with a titrated IV infusion of nitroglycerine
   d. A low CO, hypotension, normal filling pressures, with a low SVR—
      » Filling pressures should be raised by a volume load to the upper limit or even above normal
      » Inotropes and if needs be vasopressor support
   e. A low CO, hypotension, increased SVR, high filing pressures with equalization of PCWP, right ventricular diastolic and right atrial pressures—
      » Cardiac tamponade – tap pericardial fluid
3. Ensure adequate tissue oxygenation—
   – Increase DO_2 to meet tissue metabolic requirements – thereby ensure adequate $\dot{V}O_2$

Interpretation of the Hemodynamic Pattern

A hemodynamic profile can only be obtained through data obtained by invasive monitoring, generally through the use of a PA catheter. Should one hazard a diagnosis of the etiology of the shock syndrome on the basis of the hemodynamic profile? Though the cause of shock may well be suggested by the hemodynamic profile observed, this need not necessarily be so. It is wise not to always expect any particular or fixed profile in the different etiological forms of shock mentioned earlier. The etiology and the nature of circulatory disturbances causing shock in a patient should be arrived at by an overall perspective of background factors, clinical features, laboratory investigations and the hemodynamic profile observed over a period of time. The sum total of evidence is far more important than the mere consideration of the hemodynamic profile at a given point in time.

Hemodynamic Management

This is based on correct interpretation of the hemodynamic findings. A number of permutations and combinations of these variables are seen in clinical practice. Invasive monitoring, in particular the use of the pulmonary artery catheter, is not necessary in many patients. Hemodynamic measurements including CO and vascular resistance are now possible without using the PA catheter. Thus optimization of preload, and cardiac index in all forms of shock may be guided by measurement of stroke volume variation (SVV) and cardiac index by using lithium dilution (LiDCO). PiCCO is another method which allows determination of intrathoracic blood volume index, extravascular lung water index, stroke volume variation and cardiac index.[8] However, in very critical and complicated conditions, we feel that the PA catheter helps in management.

A management protocol, dependent on some of the important parameters observed, is summarized below as a guide to patient care in patients with complicated or severe shock.

- Low filling pressures (low PCWP and CVP) and hypotension. Therapy should always include a volume load to raise the filling pressures to normal or just above normal, i.e. PCWP is raised to 15–18 mm Hg. If hypotension persists, a vasopressor or dopamine is indicated.
- Low CO, hypotension and a normal SVR. If the PCWP is in the upper limit of normal or even moderately raised, a low CO deserves to be treated with inotropic support. Dopamine would be the drug of choice, as besides providing inotropic support it can increase the SVR. If the PCWP is normal, it should be pushed to the upper limit of normal or even above normal by a suitable volume load, before starting inotropic support.
- Low CO, hypotension and a raised SVR. In the presence of high, normal or raised filling pressures, inotropic support is provided by dobutamine or a combination of dopamine and dobutamine, or a combination of dobutamine and amrinone. The raised SVR in the presence of an increased filling pressure is lowered by titrated intravenous infusion of nitroglycerin.
- A low CO, hypotension, and normal filling pressures, with a low SVR. Filling pressures should be raised by a volume load to the upper limit of normal or even to a little above normal. If the CO still remains low, the use of inotropic agents is indicated; dopamine besides being an inotropic agent also increases the SVR.

Box 2 gives a summary of the abnormal hemodynamic profiles often met with in clinical practice and measures instituted for their correction.

As a general rule, vasoconstrictors must be used with caution, as they can elevate a low blood pressure but can reduce blood flow to vital organs and increase the afterload on the heart. Dopamine is the drug of choice in most instances because of its inotropic effect and a vasoconstrictor action on the peripheral circulation. Norepinephrine is preferred as first choice by some units. The use of both dopamine and noradrenaline is warranted in some patients. Dobutamine alone or with dopamine is used for inotropic support when the CO is low. Vasopressin is generally resorted to when dopamine and noradrenaline fail to produce the desired rise in blood pressure. Adrenaline infusions may also be administered particularly during resuscitation following cardiac arrest. Details of drugs used in the shock syndromes are described in subsequent chapters.

Certain points need to be stressed and recapitulated in the hemodynamic management of shock syndromes.

- As a general rule, inotropes and vasopressors should not be used unless volume replenishment is first accomplished. Perhaps in a pulseless, pressureless, well-nigh moribund shocked patient, rapid fluid replenishment and vasopressors may be perfused simultaneously for salvage, but this is a rare exception. Large volumes of fluid may need to be infused in patients with septic shock to ensure adequate circulatory volume and an adequate oxygen supply to tissues. The different fluids used for volume replacement have been discussed in the next chapter.
- Though one generally estimates an adequate intravascular volume status by filling pressures (CVP, PACP) pushed to the upper limits of normal, this estimation may be fallacious. There may well be a poor correlation between ventricular filling pressures and ventricular volumes.[9] This discrepancy may be related to a lowered compliance of the ventricles (i.e. decreased distensibility) due to a number of other possible factors, in particular increased sympathetic activity. Filling pressures may then be misleadingly high and may overestimate ventricular volumes in hypotensive patients. Therefore, if there is no evidence of pulmonary edema and if in spite of the filling pressures being pushed to the upper limits of normal, hypotension and shock persist, a bolus of 300 mL of normal saline is given quickly over 20 minutes. If the hemodynamic state, clinical picture, urine output improve and if the CVP after a brief rise comes back roughly to its original level, the patient needs to be carefully further volume loaded. If there is no change in the clinical picture and a bolus produces significant sustained rise in the CVP, further volume loading is inadvisable.[10]

A good predictor of volume responsiveness is the presence of SVV with respiration. This can be easily obtained through analysis of the arterial waveform tracing. When SVV is 9.5% or greater, a 100 mL volume load generally increases stroke volume by 5%. SVV is not useful in patients with atrial fibrillation, or in patients with multiple ectopic beats, as wide fluctuation in the baseline stroke volume is present.

An equally good dynamic test pointing to hypovolemia is a fall in the amplitude of the arterial pulse during inspiration and its rise in expiration when a patient is on ventilator support.

- If hypotension persists after an adequate volume load or if filling pressures are high to start with, inotropes and vasopressors are used, but they need to be used with caution. Very high doses of dopamine (>20–25 μg/kg) or noradrenaline (>20 μg/minute) can markedly increase

the afterload of the heart and lead to a fall in CO, thereby worsening the clinical situation. Details of inotropes and vasopressors used in the shock syndrome are described in subsequent chapters.

- The oxygen supply to tissues (DO_2) is dependent not only on the CO, PaO_2 and oxygen saturation of Hb but also on the Hb content. A low Hb must be corrected by RBC infusions. Though Hb levels of 7–9 g/dL are deemed adequate, patients with ischemic heart disease and poor cerebral circulation may require a higher Hb concentration up to 10 G% to allow an adequate DO_2.
- It must never be forgotten that however satisfactory the hemodynamic parameters, the battle for survival in shock is fought within the tissues. The DO_2 must be adequate and perhaps in some instances more than adequate if $\dot{V}O_2$ is to meet tissue demands. A persistent increase in the blood lactate level or in the base deficit are easily determined and are ominous signs of global tissue hypoxia. Lactic acidosis is best countered by improving the circulatory state. Infusions of bicarbonate have not been shown to improve prognosis and should be resorted to as a temporary measure only when the arterial pH is dangerously low (<7.2).
- Multiorgan dysfunction and failure can occur with any type of shock but is particularly observed in septic shock. Organ support is vital for survival.
- An adequate supply of oxygen to tissues is as much dependent on good lung function as on adequate CO. Almost all patients with severe shock, in particular cardiogenic and septic shock, require ventilatory support.

MULTIORGAN FAILURE AS A SEQUEL TO UNCORRECTED SHOCK

Persistent unrelieved tissue hypoxia results in impaired cell function and ultimately cellular death. The period following restoration of blood pressure and even CO to within the normal range can often be associated with continued ischemia and progressive tissue and organ damage. Postresuscitation injury is probably related to the following factors—

- *No reflow* There is persistent hypoperfusion following an ischemic insult. The mechanism is believed to be due to a calcium influx into the vascular smooth muscle during the period of ischemia, leading to intense, persistent vasoconstriction of the small vessels within various organs. This persists for hours after the blood pressure and CO are restored to normal, and results in progressive multiorgan dysfunction and multiorgan failure which carry a high mortality.
- *The development of the microcirculatory mitochondrial dysfunction syndrome (MMDS)*[11] A disturbance in the microcirculation and/or mitochondria can result in tissue hypoxia even when hemodynamic parameters are satisfactory, as has already been mentioned.
- *Reperfusion injury*[11] Reperfusion of organs after the ischemic insult leads to the distribution of toxic substances (which accumulate during the ischemic period) to various organs of the body. These toxic substances are oxygen metabolites and free oxygen radicals which readily produce widespread cellular injury.
- *Oxygen debt* During the shock state when hypotension or poor tissue perfusion is the key feature, oxygen uptake and $\dot{V}O_2$ may be inadequate for tissue needs. This represents an ongoing ischemia and it is during this ischemic period that the tissues accumulate an oxygen debt. This debt must be repaid by a compensatory period during which DO_2 and $\dot{V}O_2$ are well above normal. Patients in whom this compensatory mechanism does not occur are at greater risk of increasing cellular injury, multiple organ failure and death. In addition to the development of oxygen debt, circulatory shock results in an increase in tissue carbon dioxide, and hence an increase in the tissue PCO_2. The hypercarbonic acidosis in tissues (resulting from poor perfusion) in relation to cell and organ function may well be significant.

  The above considerations lead to an important but debatable feature in the management of severe shock states.
- *Ensuring tissue oxygenation*[9] Patients having a lower than normal $\dot{V}O_2$ have a higher mortality than those with a normal $\dot{V}O_2$. Also the $\dot{V}O_2$ may be within the normal range, yet be insufficient for tissues having an increased metabolic rate as in sepsis. An inadequate $\dot{V}O_2$ in relation to tissue needs can be determined, as mentioned earlier, by estimating blood lactate levels.

The normal lactate level in arterial blood in healthy individuals is less than or equal to 2mM/L and in stressed individuals greater than 4 mm/L. It has been shown that mortality in shock increases as lactate levels increase above 2 mm/L.[12] It has been suggested that if after the blood pressure and CO are restored the $\dot{V}O_2$ is still low (<110 mL/min-m^2), then the CO should be further increased by either volume infusion (if PCWP <18 mm Hg) or by inotropic support (if PCWP >18 mm Hg). A combination of volume load and inotropic support may be used. It has been further suggested that if the $\dot{V}O_2$ is normal or even above normal, but the lactate level is >4 mmoL/L, the CO and $\dot{V}O_2$ should be even further increased to supranormal levels, using a further volume load and/or by inotropic support of dopamine and dobutamine. Shoemaker[1] is the champion advocate of supranormal increase in CO and $\dot{V}O_2$ in shock. In his opinion, if this is achieved, survival is more likely. *Yet current opinion is that attempting to achieve supramaximal cardiac outputs and $\dot{V}O_2$ in shock does not improve survival and may even have an adverse effect.* It is possible that pushing CO and $\dot{V}O_2$ to supranormal levels may help in the small subset of intraoperative and postoperative patients who develop the hemodynamic features of shock.[1] Perhaps, the above policy is successful if it is used very early in the natural history of shock

and is unsuccessful if used later in the natural history when organ failure has already set in.

From the practical point of view, at least in the medical ICU, we have often found it impossible to raise both CO and $\dot{V}O_2$ to supranormal levels. When we have managed to do so, we have not observed any improvement in morbidity and mortality.

In conclusion, stress on adequate oxygenation of tissues in relation to their needs is probably the key factor that determines survival in severe shock states. The sooner this is achieved in the natural history of shock, the more likely are we to succeed. The difficulty lies in devising easily ascertainable accurate methods to determine $\dot{V}O_2$ and tissue oxygen requirements in critically ill patients. The practical approach of meeting the oxygen demands of the tissues in severe shock is difficult, debatable and needs further study.

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CHAPTER 14

Hypovolemic and Hemorrhagic Shock

INTRODUCTION

Hypovolemic shock[1] results from a decrease in circulating volume, which leads to a diminished cardiac output (CO) and poor tissue perfusion. The commonest cause of hypovolemic shock is trauma resulting in external or concealed hemorrhage from blunt or penetrating injuries. Blood loss into surrounding tissues following fractures of long bones or the pelvis is an important cause of hemorrhagic shock. Nontraumatic causes of bleeding constitute an important cause of hemorrhagic shock. Important nontraumatic causes include bleeding from a peptic ulcer, acute mucosal erosions, esophageal varices or from other pathologies into the gastrointestinal (GI) tract, dissection of the aorta, rupture of an aneurysm of a large vessel (e.g. a ruptured aortic aneurysm), and bleeding caused by blood dyscrasias or coagulopathies.

Hypovolemic shock is also frequently due to loss of water and electrolytes, with a fall in effective circulating volume. This is seen in burns, in vomiting and/or diarrhea from any cause,[2] in severe water loss as in diabetes insipidus, in diabetes mellitus, adrenocortical insufficiency, exfoliative dermatitis, and following excessive sweating in hot, humid climates. Sequestration of fluid with loss of effective circulating volume and hypovolemic shock can occur in intestinal obstruction, pancreatitis and peritonitis. Quick reaccumulation of a large volume of ascitic fluid after paracentesis can also occasionally lead to a fall in effective circulating volume with features of hypovolemic shock. Table 1 lists the important causes of hemorrhagic and hypovolemic shock.

Table 1: Causes of hemorrhagic and hypovolemic shock

Traumatic	*Nontraumatic*
Hemorrhagic Shock	
Blunt or penetrating injury	GI bleeds (e.g. peptic ulcer, gastric mucosal erosions, esophageal varices, typhoid bleeds, bleeds in sepsis, DIC)
Fractures specially of long bones and pelvic fractures	Aortic dissection
	Rupture of aneurysm of a large vessel, e.g. aorta
	Erosion of a large vessel, e.g. in pancreatitis or due to tumor infiltration
	Diffuse inflammation of mucosal surfaces, e.g. ulcerative colitis
	Blood dyscrasias or coagulopathies
Hypovolemic Shock	
Burns	Fluid loss from vomiting and/or diarrhea, e.g. in cholera, other GI infections
Crush injuries	Fluid loss in diabetes mellitus, adrenal insufficiency, excessive sweating, exfoliative dermatitis, diabetes insipidus, reaccumulation of ascites after tapping
	Sequestration of fluid, e.g. in intestinal obstruction, pancreatitis, peritonitis

Abbreviations: GI, gastrointestinal; DIC, disseminated intravascular coagulation.

PATHOPHYSIOLOGY[1,3,4]

Hypovolemia from any cause, if severe and untreated, causes increasingly poor perfusion of tissues, ischemia and injury to tissue cells, and ultimately death.

A fall in circulating volume leads to decreased venous return, decreased filling pressures on the right and left sides of the heart and a decreased CO, which leads to tissue hypoxemia. The loss of intravascular volume initiates several compensatory mechanisms, the ultimate purpose of which is

directed towards maintaining perfusion of vital organs such as the heart and the brain. The effectiveness of these mechanisms is dependent on the rate of fluid loss and the degree of volume depletion present.

Neurohormonal Compensatory Mechanisms

Volume depletion stimulates baroreceptors within the intrathoracic vessels and the carotids, as also organ-specific baroreceptors within the kidneys resulting in an increased sympathetic discharge, increased release of stress hormones like catecholamines and cortisol, increased secretion of antidiuretic hormone and activation of the renin-angiotensin system. Activation of the renin-angiotensin aldosterone system leads to conservation of sodium by the kidneys. The sodium and water that are retained help to increase circulating blood volume. The retained sodium is also distributed uniformly in the extracellular fluid, thereby replenishing the interstitial fluid deficit caused by the intracapillary refill, as explained in the next section.

The increased sympathetic discharge leads to tachycardia, increased systemic vascular resistance (SVR), maintenance of systemic blood pressure, and maintenance of perfusion to the brain and the heart at the expense of perfusion to other organs (skin, muscles, kidneys, gut).

Shift of Fluid from the Extravascular to the Vascular Compartment[1]

Total body water comprises 60% of the lean body weight (or 600 mL/kg) in man and 50% of the lean body weight (or 500 mL/kg) in woman. Fifty-five percent of the total body water is intracellular and 45% extracellular. The interstitial fluid content is 20% of the total body water, while plasma constitutes just 7.5% of total body water, and in a 70 kg male amounts to 3–3.2 liters.[1] With a hematocrit of 45%, the blood volume in a 70 kg male would be about 5.5–5.7 liters (or 66 mL/kg) and in a female would be about 60 mL/kg. The blood volume thus constitutes just 13% of the total body fluids. Ordinarily, an acute loss of 35–40% of the blood volume can be fatal, which means that human survival is determined by about 4% of the fluid in the body.[1] Therefore, to reduce mortality, it is imperative to prevent a bleeding patient from losing this 4% fluid volume.

Besides the neurohormonal compensatory mechanisms, shift of fluid from the interstitial compartment into the vascular compartment helps in some measure to restore blood volume in hemorrhagic shock. This occurs in three phases (Fig. 1).

Phase 1 Within an hour of blood loss, there is a shift of fluid from the interstitial compartment into the capillaries. This continues for 40 hours and the volume shift can be as high as one liter. The interstitial compartment however stands depleted due to this shift.

Phase 2 A depleted blood volume activates the renin system, leading to sodium retention. Sodium diffuses into the extravascular compartment, and the retained sodium leads to water retention, thus helping to replenish the interstitial fluid.

Phase 3 Blood loss stimulates erythropoiesis within a few hours. Between 15–50 mL of cell volume is produced daily, and complete replenishment of depleted cells takes as long as 2–3 months.

The neurohormonal changes described above and the shift of interstitial fluid into the vascular compartment work hand in hand to preserve tissue perfusion, particularly to vital organs. Compensatory mechanisms however can only work up to a point. They can maintain an adequate blood volume if blood loss is less than 15% of total blood volume. A larger volume loss (>15% of total blood volume) if not adequately and quickly replaced, inevitably leads to tissue ischemia and metabolic acidosis. Tissue damage results and this induces cellular and humoral inflammatory responses which further exacerbate circulatory abnormalities that ultimately lead to irreversible widespread cell injury and death. The importance of early restoration of a depleted blood volume by vigorous infusions of intravenous fluids cannot be overstressed, if hemorrhagic and hypovolemic shocks are to be reversed.

CLINICAL FEATURES[3,4]

Clinical features of hemorrhagic and hypovolemic shock are similar, and depend on the age of the patient, pre-existing background medical problems, the degree of volume loss, the time period over which the volume loss has occurred, and the ability of a patient to bring the compensatory mechanisms outlined above into play.

A young previously healthy individual may suffer a loss of 10% to as much as 15% of the blood volume with few or no clinical symptoms and signs, since the blood volume is quickly replenished by transcapillary refill. An elderly individual

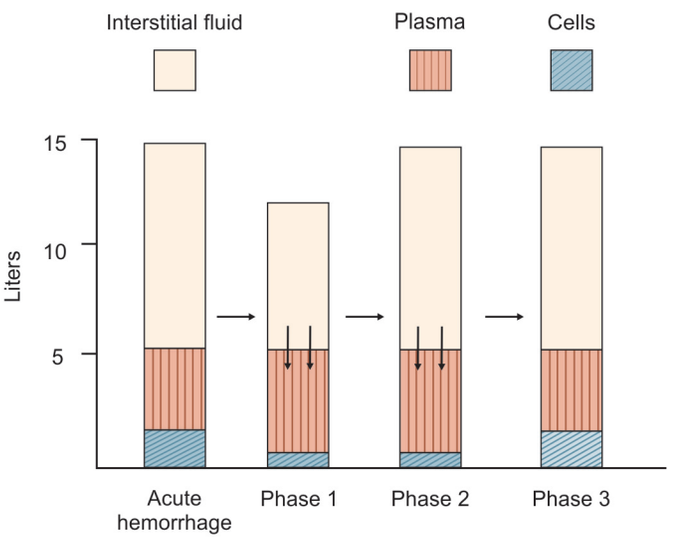

Fig. 1: Response to mild hemorrhage. Phase 1: Shift of fluid from interstitial fluid compartment into capillaries with decrease in volume of the interstitial fluid compartment. Phase 2: Depletion of blood volume activates the renin system, resulting in sodium retention, water retention and replenishment of interstitial fluid compartment. Phase 3: Erythropoiesis stimulation due to blood loss

Source: Modified from Marino PL. The ICU Book, Lippincott Williams & Wilkins; 1991.

or one who is critically ill, or who has a background of cardiopulmonary problems or has a hemoglobin (Hb) less than 8 g/dL to start with, will manifest symptoms and signs with blood loss of as little as 350–400 mL. The first manifestation of an abrupt occult blood loss of as little as 300 mL in a critically ill patient in the intensive care unit (ICU) is a worsening of his overall critical state with regard to his vital signs and urine output. The reason for this worsened state can easily be missed.

The early clinical features of blood loss exceeding 500–700 mL include tachycardia, pallor, a heightened anxiety and restlessness. Tachycardia may be mild or even absent (except when the blood loss is acute) in young individuals with a blood loss of less than 500 mL. The skin may be cold and clammy. Sudden, inexplicable, profuse sweating may be the first symptom or sign of an occult or fairly severe blood loss as in an upper GI bleed. Unless blood or volume loss is very severe and acute, the blood pressure is often initially maintained. Even so, orthostatic hypotension may be demonstrated by a drop in systolic blood pressure more than 10 mm Hg on changing from the supine to the sitting posture and more than 20 mm Hg on changing from the supine to the standing posture, the postural fall in blood pressure being often accompanied by a complaint of dizziness. The neck veins are collapsed, unlike patients in cardiogenic shock where the neck veins are full. Oliguria is present (urine output <0.5 mL/kg per hour), and may progress to complete anuria.

Compensatory mechanisms in severe shock ultimately fail. The systolic blood pressure then drops and the patient's mental state may get progressively obtunded. In many patients, the systolic blood pressure is maintained (between 100 and 120 mm Hg) in spite of significant blood loss. This should never lull the physician into a false sense of complacency. When the blood pressure does fall in these patients, it crashes precipitously, frighteningly to unrecordable levels, with disastrous consequences. In hemorrhagic shock, a significant drop in pressure (>30 mm Hg) in the supine position, together with marked oliguria, suggests a loss of more than 30% of blood volume, or an effective loss of about 2L in a 70 kg patient. By this time, tachycardia is invariably present, the pulse being feeble and thready. In patients who have a poor sympathetic drive (as in the elderly) the degree of tachycardia is much less marked in relation to the degree of blood loss. Bradycardia may be observed terminally in such patients. Increasing metabolic acidosis is the classic sign of increasingly poor tissue perfusion. Towards the end, the patient is pulseless, pressureless and almost anuric. If cerebral perfusion is preserved, the patient may remain alert; more often than not, he is obtunded and confused.

Four categories of blood loss have been tabulated in Table. 2. Compensatory responses chiefly in the form of tachycardia and vasoconstriction may be blunted in elderly patients, diabetics, alcoholics, in patients with chronic renal and liver cell dysfunction, and in patients enfeebled by debilitating illnesses. Tachycardia may be less marked or even absent in these situations, and hypotension may occur early with little blood loss.

Monitoring Hypovolemic Shock[1]

Clinical monitoring of vital parameters, like the pulse, blood pressure, respiratory rate, skin and core temperature, capillary refill, urine output, oxygen saturation, jugular venous pressure, arterial pH and blood gases, is essential. An arterial line is indicated if the blood pressure is low, as otherwise false very low readings are obtained with the noninvasive blood pressure measurement technique.

Monitoring the hematocrit, the hemodynamic pattern, oxygen supply to tissues (DO_2), oxygen consumption ($\dot{V}O_2$), oxygen extraction, and the end-tidal CO_2 are briefly described below. It needs to be mentioned, particularly for our part of the world, that it is not always necessary to measure oxygen extraction DO_2,$\dot{V}O_2$ and end tidal CO_2 for the proper management of hypovolemic shock. Even the pulmonary artery catheter to monitor the hemodynamic profile is being used with increasing infrequency. Yet there are occasions when these measurements are of help to understand the nature of a difficult problem confronting the intensivist.

Hematocrit[1,5]

It is important to remember that acute blood loss produces no immediate change in the Hb, red blood cells (RBCs) count, or the hematocrit. This is because if whole blood is lost, the

Table 2: Classification of hemorrhage[3]

Parameters	*Class*			
	I	II	III	IV
Blood loss (mL)	<750	750–1,500	1,500–2,000	>2,000
Blood loss (%)	<15	15–30	30–40	>40
Pulse rate (beats/min)	<100	>100	>120	>140
Blood pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate (breaths/min)	14–20	20–30	30–40	>35
Urine output (mL/hour)	>30	20–30	5–15	Negligible
CNS symptoms	Normal	Anxious	Confused	Lethargic

Abbreviation: CNS, central nervous system.

Source: Modified from Committee on Trauma.[3]

concentration of RBCs, Hb and the proportion of RBCs to plasma remains unchanged. It may take 24 hours or more for sufficient interstitial fluid to enter the vascular compartment and significantly reduce the Hb and the hematocrit. On the other hand, if the patient has bled slowly, if recognition of blood loss is delayed, or if fluid resuscitation has been prompt, the hematocrit will be low. When hypovolemia results from loss of fluids as in vomiting, diarrhea, fistulae involving the GI system, or in sequestration of fluids as in intestinal obstruction, the hematocrit is high.

Hemodynamic Pattern

The classic hemodynamic pattern (also see Chapter Overview of Shock Syndromes) is a low central venous pressure (CVP), a low pulmonary capillary wedge pressure (PCWP), a low CO and a high SVR. Tachycardia is generally, though not always present, and the blood pressure may be maintained within normal limits because of compensatory increase in SVR. It is important to interpret hemodynamic findings with circumspection and not necessarily let them take precedence over clinical findings. The filling pressures and, in particular, the CVP are not always very reliable in assessing the degree of volume loss in critically ill patients. The following features may interfere with the correct interpretation of the clinical state—

- The CVP is influenced by the compliance of the veins and of the ventricles, and both these may be decreased by hypovolemia. The excessive venoconstriction resulting from sympathetic activation may produce a higher CVP than is expected with the degree of volume loss.
- Higher than expected CVP readings are observed if vasopressors have been used to counter hypotension. This is not uncommon when the etiology of hypotension has been incorrectly diagnosed.
- Higher than anticipated CVP readings may also be observed when the hypovolemia is associated with cardiac tamponade or a tension pneumothorax (as in severe trauma).
- A CVP below +2 cm H_2O signifies volume depletion. However, the CVP is ordinarily low (between 2–10 cm H_2O), and there is little margin for change with hypovolemia. Single pressure readings at a given point in time can be misleading. It is important to interpret changes in trends in pressure readings over a period of time, particularly after fluid resuscitation has commenced, and to correlate these changes with improvement in clinical findings.

Oxygen Extraction[1,3]

According to Fick's principle (see Chapter Basic Cardiorespiratory Physiology in the Intensive Care Unit), the usual response to a lowered CO is an increase in oxygen extraction from the blood perfusing the tissues. This can continue only to a point (where 50% oxygen has been extracted from the arterial blood) after which an oxygen debt occurs and tissue metabolism switches from aerobic to anaerobic. Ideally, mixed venous oxygen saturation and pressure are estimated from blood samples withdrawn from the pulmonary artery via the pulmonary artery catheter. However, blood samples are now generally drawn from a central venous line, on the assumption that the results of central venous oxygen saturation ($ScvO_2$) thus obtained are close to those obtained by the more accurate estimation of mixed venous oxygen saturation ($S\dot{v}O_2$) of blood drawn through a pulmonary artery catheter (see Chapter Overview of Shock Syndromes). Specially devised central venous catheters can give a continuous display of $ScvO_2$ readings on the monitor.

The expected changes in oxygen extraction and $S\dot{v}O_2$ in hypovolemia progressing to hypovolemic shock are given below.

	SaO_2 (%)	*$S\dot{v}O_2$ (%)*	*O_2 extraction (%) (SaO_2–$S\dot{v}O_2$)*
Normal	>95	65–70	about 30
Hypovolemia	>95	50–65	30–50
Shock	>95	<50	>50

An increasing difference between SaO_2 and $S\dot{v}O_2$ is ominous and a difference over 50% generally denotes shock with tissue hypoxia.

End-Tidal CO_2

A decrease in CO results in a decrease in partial pressure of carbon dioxide (PCO_2) of the expired gas. This is a simple method of monitoring a falling CO in hypovolemic shock. The end-tidal CO_2 is normally 3–4 mm Hg less than the partial pressure of CO_2 in the arterial blood. It may drop to below 10 mm Hg in severe shock and shows a progressive rise with successful volume resuscitation. End-tidal PCO_2 can be measured and monitored using standard nasal cannula used to provide oxygen to the patient.

DIFFERENTIAL DIAGNOSIS

Hypovolemic shock may be mistaken for shock due to other causes if bleeding or fluid loss is not externally evident. Cardiogenic shock has similar features except that it is usually associated with distended neck veins. Spinal injury following trauma may produce vasodilatation which is relatively refractory to fluid administration. Shock following trauma is however invariably due to hypovolemia, and other causes should only be entertained after adequate fluid replacement therapy has first been instituted. A state of shock can occur following hypoglycemia due to excessive insulin administration. The patient is cold, clammy, has tachycardia and may be hypotensive. Brainstem signs and decerebrate states when present are seen more frequently in hypoglycemia than in hypovolemic shock. A history of insulin administration should always arouse suspicion. After blood has been sent for glucose estimation, administration of 50 mL of 50% dextrose should promptly produce marked improvement in the patient's condition. The picture of hypotensive shock is also observed in patients with well-marked adrenocortical insufficiency. Mere replacement of volume is not enough for resuscitation. Hydrocortisone 100 mg IV 8 hourly is mandatory

for survival. In fact the persistence of marked hypotension after adequate volume replacement should always raise the possibility of an underlying adrenocortical insufficiency.

MANAGEMENT[1,3]

The principles of management are as follows—

I. Fluid resuscitation. Rapid fluid resuscitation is the keystone of therapy in hypovolemic (including hemorrhagic) shock. Restoring the volume within the vascular compartment increases venous return, increases and supports CO, raises blood pressure and improves tissue perfusion. It reverses the effects of hypovolemic shock.

II. Replacement of Hb with blood transfusions when shock is due to significant blood loss.

III. Monitoring fluid and blood resuscitation clinically, and re-evaluating the overall condition after initial fluid resuscitation. CVP monitoring is essential; in difficult cases (see below), hemodynamic monitoring through a Swan-Ganz catheter may further help management.

IV. Determining the etiology of hypovolemic shock and treatment of the cause in so far as this is possible. In hemorrhagic shock without external bleeding, it is important to determine the site of blood loss and arrest a continuing bleed. External hemorrhage should be controlled by prompt pressure over the site, and surgical control of the bleed. One should never wait for laboratory tests, but should start fluid resuscitation promptly. Investigations to determine the cause of severe hypovolemic shock are carried out after, or pari passu with emergency resuscitation.

I. Fluid Resuscitation[6]

Principles

The ultimate objective in fluid resuscitation is to restore and maintain O_2 uptake in vital organs of the body so as to preserve organ function.

$$\dot{V}O_2 = CO \times (CaO_2 - CvO_2)$$

where, CaO_2 is oxygen content of arterial blood and CvO_2 is oxygen content of venous blood.

In acute severe fluid loss it is the CO alone which needs to be urgently restored and sustained. In severe acute blood loss, $\dot{V}O_2$ is compromised both by a low CO and a low Hb. Unquestionably a low CO has far more dangerous consequences than anemia. The prime objective therefore in shock due to acute blood loss is to first restore CO and improve blood flow; correcting Hb deficit is the next objective. Therefore, in severe hypovolemic or hemorrhagic shock, fluids should be infused rapidly to quickly correct the volume deficit and thereby increase CO and blood flow. In young, previously healthy patients, the infusion in severe hypovolemic shock is given at the maximal rate through a large bore (14–16 gauge) catheter used to cannulate a vein. In older patients, or in those with cardiac disease, the infusion should be given less rapidly with a close watch for hypervolemia and complicating pulmonary edema.

Cannulation Site

In severe shock, it is mandatory to have access to two veins through two large bore (16 gauge) intravenous catheters. Central venous catheters do not permit rapid fluid replacement in severe hypovolemic shock, because of their long length and because the lumen of the usual central lines is too small to allow rapid fluid flow (see below). It is best therefore, to insert a short 14–16 gauge catheter into a peripheral vein. If this is impossible because of totally collapsed peripheral veins, a large bore catheter can be placed in the femoral vein, or a central line necessarily has to be secured.

Catheter Dimensions and Relation to Flow Rate

The maximum infusion rate is dependent on the size (i.e. lumen) of the catheter, and not on the size of the vein that is cannulated. To be more precise, the infusion rate is directly related to the pressure gradient along the catheter, and the fourth power of the radius of the catheter. It is inversely related to the length of the catheter and the viscosity of the fluid infused. The relationship stated above is illustrated in Table 3. It is to be noted that the infusion rate is almost four times greater in the 2" short peripheral 14 gauge catheter, than in the usual 12" long central venous catheter. Table 3 illustrates the importance of the short 2" peripheral catheters for rapid infusions and quick fluid replacement, as compared to the long central venous catheters.

Use of introducer catheters in central veins. Marino[1] has correctly stressed that the adverse effect of catheter length on infusion rate in central venous cannulation, can be overcome by the use of large bore introducer sheath catheters. These introducer sheaths in sizes of 8.5 Fr (2.7 mm internal diameter), and 9 Fr (3 mm internal diameter) are normally used as conduits for multi-lumen catheters or the Swan-Ganz catheters, but can be used by themselves for rapid volume replacement.

Relation of Fluid Viscosity to Flow Rate

Studies have shown the influence of viscosity on flow rates (Table 4). It was shown that the infusion rates of water

Table 3: Influence of catheter size on infusion rate

Infusion device	*Length (inches)*	*Flow rate* (mL/min)*
9-Fr introducer	5½	2407
IV Extension tubing	12	220
Peripheral		
14-gauge catheter	2	195
16-gauge catheter	2	150
Central		
16-gauge catheter	5½	91
16-gauge catheter	12	54

*Gravity flow of tap water

Source: Mateer JR, Thompson BM, Aprahamian C, et al. Rapid fluid resuscitation with central venous catheters. Ann Emerg Med. 1983;12(3):149-52.

and 5% albumin were similar. The infusion rate of whole blood was slower and that of packed RBCs was the slowest. The importance of using crystalloids and/or colloids for emergency fluid replacement is therefore evident.

Estimating Volume Requirements in Hypovolemic Shock

There is always a tendency to underestimate volume or blood loss in hypovolemic shock. The following approach has been proposed by Marino[1] for a rough estimation of fluid loss—

i. Estimate normal volume In adults the normal blood volume is estimated at 66 mL/kg for males, and 60 mL/kg for females. Lean body weight is used for this estimate. For obese patients, the blood volume is first estimated on the actual body weight and 10% is then subtracted from the value obtained initially.
ii. Estimate the percentage of volume that is depleted This is calculated according to the classification system tabled earlier (Table 2).
iii. Calculate the volume deficit This is done by multiplying the estimated normal blood volume and the percent lost. This quantifies the volume that requires to be replaced.
iv. Resuscitation with reference to the fluids used The volumes are estimated roughly as follows—
   - If whole blood is used for resuscitation, then the volume to be replaced is 1 × volume deficit.
   - If colloids are used for fluid resuscitation, then the volume necessary is 1 × volume deficit.
   - If crystalloids (normal saline, Ringer lactate) are used for fluid resuscitation, the volume that needs to be infused is 3 × volume deficit.

Fluids Used in Volume Replacement

Shoemaker[7] studied the ability of different resuscitation fluids to promote CO. Each of the fluids was administered over an hour and the change in cardiac index was noted at the end of infusion. The resuscitation fluids studied were whole blood (500 mL), packed cells (500 mL), dextran-40 (500 mL), Ringer lactate (1L). The infusion volumes of whole blood, packed RBCs, dextran-40 was similar (500 mL); the infusion volume of Ringer lactate was twice that of the other fluids. Figure 1 shows that the maximum increase in cardiac index was observed with the colloid dextran-40, the next with whole blood, then with Ringer lactate and the least (little or no increase) with packed RBCs. The obvious inference was that colloids were superior to blood products and crystalloids for increasing CO and blood flow. Also, erythrocyte concentrates should not be used to increase blood flow. As has already been stated, the volume of crystalloid fluid should be three times greater than the volume of colloid infusion. Even so, there is still debate as to whether crystalloids or colloids should be used for emergency fluid resuscitation. The colloid-crystalloid controversy is discussed later in this chapter.

Table 4: Influence of fluid type on infusion rate

Fluid	*Flow rate (mL/min)**
Tap water	100
Albumin (5%)	100
Whole blood	65
Packed cells	20

*Gravity flow through a 16-gauge, 2-inch catheter.
Source: Dula DJ, Muller HA, Donovan J. Flow rate variance of commonly used IV infusion techniques. J Trauma. 1981;21(6):480-2.

Most units generally use rapid infusions of crystalloids, either normal saline or Ringer lactate. In our country as also in other developing countries, these fluids are cheap, readily available and provide quick though transient intravascular expansion. When signs and symptoms of shock are apparent, 2 L of crystalloid solution is administered to the adult, and 20 mL/kg to a child. As quick equilibration occurs with the extravascular fluid compartment in about 30 minutes, only 25% of the infused fluid can be presumed to remain in the vascular compartment after an infusion of crystalloids. Hence the rough rule that the volume to be replaced is at least three times the volume deficit as calculated in the manner described earlier.

Colloid solutions are equally effective for volume replacement and can increase the cardiac output (CO) more quickly than crystalloid solutions.[7] Colloid solutions in our country are however extremely expensive and in smaller district hospitals not easily available. When hypovolemic shock is associated with marked hypotension, crystalloid solutions can be infused through one vein and colloid solutions can be infused through another. The colloid solution helps to augment CO and blood pressure quickly while the crystalloids further help to correct the sodium loss in the extracellular compartment which is an invariable feature of moderate to severe hypovolemic shock.

Currently studies based on large randomized trials seem to suggest that colloids hold no advantage over crystalloids and that crystalloids alone can be used for resuscitation from hypovolemic shock.

The major complication associated with the use of crystalloid solutions is either underhydration due to inadequate volume replacement, or overhydration resulting in a hypervolemic state. Excessive administration of crystalloids can result in generalized edema. Pulmonary edema is however rare in previously healthy individuals unless overinfusion results in a sharp increase in the PCWP to more than 25–30 mm Hg. A careful monitoring of pulmonary hydrostatic pressure (PCWP) particularly in patients with underlying cardiorespiratory disease is helpful and should prevent this complication. Since the chloride concentration of normal saline is significantly higher than the chloride concentration of plasma, patients resuscitated with large infusions of normal saline develop a hyperchloremic metabolic acidosis which requires renal excretion of chloride for correction. After infusing the first 1.5–2 liters as normal saline in severe hypovolemic shock, normal saline with either Ringer lactate solution or 5% dextrose saline are used alternatively for further correction of the volume deficit. Ringer's solution is preferred

to normal saline infusions in some units for replacing volume deficits. Ringer's solution has a more physiological electrolyte content; the lactate within it is converted to bicarbonate by the liver, except in very ill patients or in those with marked hepatic dysfunction.

It is important not only to replace volume, but also to ensure that the concentration of electrolytes in plasma is kept normal. Hypokalemia is very frequent in hypovolemia produced by vomiting, diarrhea, by fluid loss from fistulae involving the GI tract, or by sequestration of fluids within the gut. Between 40–60 mEq of potassium (K^+) in a dextrose or dextrose-saline infusion are given over 4 hours through a separate vein and repeated if necessary after monitoring serum K^+ levels. *It is a mistake to give large volumes of 5% dextrose for fluid resuscitation as severe hyponatremia results, and this may be difficult to correct against a background of shock.*

Occasionally hypovolemic shock due to vomiting and diarrhea is associated not only with a severe hypokalemia, but also by excessive loss of bicarbonates in the stools with a resulting metabolic acidosis. Cholera (due to the Gram-negative *Vibrio cholerae*), is a classic example where severe hypovolemic shock due to fluid loss from vomiting and diarrhea, is associated both with hypokalemia and metabolic acidosis and with low plasma bicarbonate levels. Intravenous fluid replacement is best undertaken by using a special solution containing 5 gm sodium chloride, 4 gm sodium bicarbonate and 1 gm potassium chloride in 1 liter of distilled water. If the above solution is not available, infusion of 1 liter of isotonic saline is alternated with 500 mL of either isotonic sodium bicarbonate (1.4% in 500 mL), or 1/6th molar sodium lactate. This is continued till volume replacement is judged adequate. In fulminant cases with uncontrolled vomiting, and the continuous passing of large volume rice water stools, 10–12 liters of fluid may need to be replaced in the first 12 hours. Potassium losses may need to be separately replaced in a dextrose-saline drip. The patient needs critical care, but it is advisable to provide this in an isolation ward rather than in an all-purpose critical care unit. Fluid and electrolyte replacement as outlined above, and tetracycline 500 mg four times a day for 10 days, form the cornerstones of therapy. Oral rehydration therapy is both cheap and extremely effective in moderately severe cases. The solution used orally, if necessary through a nasogastric tube, should contain glucose 30 gm, sodium chloride 3.5 gm, and potassium bicarbonate 2.5 gm in 1 liter of water. The rate of administration is 750 mL/hour for patients weighing over 25 kg, and 500 mL/hour for patients weighing less than 25 kg.

Colloid-Crystalloid Controversy

The question that needs to be answered is—should colloids be used at all in the resuscitation of patients in shock, including patients in hypovolemic shock?

The colloids in use are albumin (5% and 20%), a gelatin preparation marketed as Haemaccel and hydroxyl-ethyl starch (HES). Dextrans though powerful plasma expanders are now hardly ever used because of their untoward reactions—chiefly anaphylaxis, renal dysfunction and bleeding. Dextran inhibits platelet adhesion and aggregation, producing a clinical effect similar to von Willebrand's disease. Hydroxy-ethyl starch is infrequently used in our country. It can cause renal dysfunction from starch being deposited in renal tubule cells. We chiefly use albumin, and at times the gelatin solution—Haemaccel.

In theory, colloids because of their increased osmotic pressure and their low permeability through capillary walls should produce quick volume expansion and a quicker increase in cardiac output (CO) as compared to crystalloids. Yet all prospective randomized clinical studies, as also a meta-analysis, maintain that there is no advantage in the administration of colloids as compared to crystalloids for resuscitation from all forms of shock.[8-10]

In 2004, a large randomized control study of normal saline versus 4% albumin for resuscitation in the ICU showed no difference in mortality between the two groups. In another blinded randomized controlled study called the crystalloid versus hydroxyl ethyl starch (HES) trial (CHEST)[9] involving 7,000 adults in the ICU, the use of HES compared to N-saline resulted in no difference in mortality between the two groups. In fact HES has some degree of nephrotoxicity and was associated with a 21% increase in the rate of renal replacement therapy.

Current evidence points to the lack of clinical benefit, potential nephrotoxicity of colloid infusions, and to this is added the increased cost of semisynthetic colloids and albumin. Hence is the use of colloids for resuscitation in shock justified? In spite of evidence to the contrary, colloids continue to be widely used, particularly so in disaster situations, and for resuscitation of the wounded in times of war or conflict. We need to consider certain aspects of the controversy and perhaps use colloids only in certain situations.

1. Every large study has randomly given to patients either colloids or crystalloids. This need not be so in practice. Crystalloids are always given and continued till resuscitation is complete. Colloids should not be solely used for volume replacement and resuscitation. They could however be used with advantage in the following circumstances—
   a. In severe hypovolemic shock with a barely palpable pulse and a barely recordable blood pressure, crystalloids and colloids are started simultaneously (through separate veins). A quicker restoration of blood volume, a rise in CO and blood pressure and a quicker improvement in tissue perfusion is observed. Once the circulatory state has improved, crystalloids are continued and colloids are stopped. The volume of colloids used is then much less than that reported in clinical studies.
   b. In fluid resuscitation for severe burns patients, infusions of IV albumin are used after 24 hours to minimize the formation of edema and water-logging of tissues which would result from further continued administration of large volumes of crystalloids.

c. After resuscitation of severe hypovolemic shock with large volumes of crystalloids, colloids may be used in patients who are water-logged as judged by marked pitting edema over the feet and legs. The increased plasma oncotic pressure mobilizes extravascular fluid into the vascular compartment, the extra fluid being then excreted by the kidneys.

If colloids are used as stated above, the question of solely choosing one (colloid) or the other (crystalloid) does not arise. The controversy would still continue but perhaps in a lower key! It needs to be remembered that the large randomized trials on colloids and crystalloids contained a mixed group of patients with different background factors leading to shock and the need to resuscitate. No study comparing equivalent cohorts has been done. Nor is there a randomized study comparing a cohort of patients receiving crystalloids and colloids with another equivalent cohort receiving only crystalloids. To my mind, no further studies on colloids versus crystalloids are really necessary. Evidence is always welcome and valued but it should not usurp clinical judgment.

II. Monitoring Fluid Replacement and Endpoints in Therapy

Volume replacement by fluids should reverse shock. Clinical parameters, such as a fall in heart rate, increase in blood pressure, restoration of urine output, increased warmth of the skin with evidence of improving or good capillary refill, should be taken into account to determine the adequacy of volume replacement. Restoration of the mental state to normal, and correction of metabolic acidosis are good indicators of improving circulatory function. Correction of metabolic acidosis is gauged by a return of serum lactate to less than 2 mmoL/L and an abolition of the base deficit if the lactate levels and base deficits were increased prior to resuscitation.

Volume replacement is guided by—

- An improvement in the circulatory and metabolic state.
- Monitoring filling pressures which may be increased to the upper limit of normal. It should however be noted that the filling pressures for various reasons cannot always be equated with ventricular volume, so that a patient may require further volume replacement in spite of adequately raised filling pressures (see Chapter Overview of Shock Syndromes).
- A normal $\dot{V}O_2$. This need not be measured in every patient but is a useful marker in critically ill hypovolemic patients.

The quantum of volume replacement to start with should be guided by but not solely determined by the estimated volume loss (Table 2). This is particularly important in hemorrhagic shock in older patients. Severe blood loss causing shock in these patients is associated with a marked compensatory increase in venous tone. Blood transfusions to replace lost blood ordinarily reverse shock and simultaneously cause a reduction in venous tone. However, in some patients the venous tone remains persistently high. An increasing volume in the vascular compartment in association with a raised venous tone can cause a rise in the filling or right atrial pressures to above normal, even when volume replacement is incomplete. In young individuals with normal hearts, this does not usually matter. In older individuals with poor depressed left ventricular function curves, a rise of right atrial pressure by even 3–4 mm Hg above normal can induce a threefold or even greater increase in the left ventricular filling pressure. The latter may rise from 8 to 24 mm Hg or even 30 mm Hg, and cause acute pulmonary edema.

Over-infusions resulting in pulmonary edema can be clinically detected by noting an increased respiratory rate, by careful auscultation for crackles at the lung bases, and by pulmonary congestion which is evident on a chest X-ray. Detailed hemodynamic monitoring of PCWP, CO, SVR through a pulmonary artery catheter is not indicated or necessary in most patients. In fact many units prefer to treat all forms of shock as far as possible without the use of the PA catheter. Invasive hemodynamic monitoring is however helpful in the following circumstances—

- When hypovolemia complicates other forms of shock, e.g. septic or cardiogenic shock.
- When the cause of shock is not clearly evident.
- When hypovolemic shock occurs in patients with known poor cardiac function, or in patients with suspected myocardial dysfunction.
- When during fluid replacement, pulmonary congestion is evident, even though the replaced volume seems to be inadequate.
- In patients where the CVP is persistently higher than expected in the face of shock.
- In patients where inotropic support is required even after adequate volume replacement.
- The endpoint of volume replacement with hemodynamic monitoring is to maintain a PCWP around 15 mm Hg and a CVP within the normal range.

$\dot{V}O_2$ and Serum Lactate

In individuals with severe hypovolemic shock, volume repletion may still be associated with persistent tissue ischemia, either due to the severity of the shock to start with, delay in resuscitation, to the presence of the microcirculatory mitochondrial dysfunction syndrome or perhaps to reperfusion injury. In patients where clear evidence of one or more organ dysfunction persists after volume replacement, $\dot{V}O_2$ and serum lactate measurements should be monitored. If the $\dot{V}O_2$ is found low and the serum lactate measurements are more than 4 mm/L, further volume infusions with or without inotropic support is advocated.

Vasopressors are not indicated in pure hypovolemic shock. If however hypovolemic shock is complicated by myocardial infarction, or poor myocardial function, inotropic agents may be used after volume repletion is complete. Vasopressors with or without inotropes may be necessary if hypotension and poor tissue perfusion persist in spite of complete replenishment of circulatory volume. A fall in filling pressures after fluid replacement with a relapse into a shocked state, should suggest continuing fluid or blood loss. A persistent need for vasopressors or inotropic agents after fluid resuscitation

should also alert the physician to continuing volume loss or myocardial infarction, and in patients with traumatic shock, to pump failure from myocardial contusion, cardiac tamponade or aortic dissection. The clinical features, relevant investigations and response to therapy should help to detect these problems.

III. Replacement of Hb in Shock Due to Blood Loss

Once depleted volume has been replaced, and CO and blood pressure supported by fluid resuscitation, the lost Hb should be replaced, with packed RBC infusions. Neither the hematocrit value nor the Hb concentration is an accurate representation of the total erythrocyte volume in the blood after fluid replenishment. The hematocrit and the erythrocyte volume will fall with an increase in plasma volume (as after fluid replenishment). The hematocrit will remain unchanged even with a change in erythrocyte volume when there is a proportionate change in plasma volume, as after acute blood loss or after transfusion of whole blood. For practical purposes any estimated blood loss approaching 20% or more will require a correction of anemia with the use of packed RBCs, the Hb concentration being kept at approximately 10 g/dL. This increases the oxygen carrying capacity of blood and helps tissue oxygenation. Though probably true for many patients, it may not necessarily be so for all.

McCormick and associates studied the influence of an increase in CO and an increase in hematocrit by blood transfusions on oxygen uptake by tissues ($\dot{V}O_2$) during resuscitation from hemorrhagic shock.[11] They noted that the $\dot{V}O_2$ increased after the CO was raised, but did not increase when the hematocrit was raised by blood transfusions. This may well be possible if the $\dot{V}O_2$ is on the flat portion of the curve relating oxygen delivery to oxygen consumption. Marino[1] is of the opinion that indications for transfusions in normovolemic patients are: (i) $\dot{V}O_2$ below the normal range; (ii) Blood lactate levels more than 4 mmoL/L; (iii) Oxygen extraction ratio more than 0.5. To physicians practising in poor countries, these conditions for infusing packed cells in hemorrhagic shock (after restoring fluid volume and CO) are impractical. We strongly feel that the traditional dictum of maintaining the Hb at around 10 g/dL holds true.

In patients with continuous profuse bleeding as in severe trauma, massive surgery, blood dyscrasias, coagulopathies, whole blood transfusions and fluids are used simultaneously to counter severe hemorrhagic shock. For every three units of blood given, the patient should be given a unit of fresh frozen plasma. Massive whole blood transfusions can cause or worsen a coagulopathy.

IV. Determining and Treating the Etiology of Hypovolemic or Hemorrhagic Shock

In the tropics and in poor developing countries, cholera is an important cause of acute vomiting and diarrhea. *Salmonella* infections or violent GI infections with Gram-negative organisms (in particular *Klebsiella* or *E. coli*), can also cause severe hypovolemic shock. Relevant investigations and specific treatment are available for such infections (see Section Fever and Acute Infections in a Critical Care Setting).

Profuse hemorrhage from the GI tract may produce profound collapse, and if the patient does not have hemetemesis or obvious bleeding per rectum, the source of bleeding may not be evident for as long as 24 hours. A rectal examination in these patients often reveals the presence of malaena by the jet black stools staining the examining finger. Hemorrhage from a leaking aneurysm may be missed if a careful clinical examination has not been performed.

Definitive therapy might first require diagnostic studies after the patient has been resuscitated and stabilized. Important diagnostic techniques to detect the site of the GI bleed are endoscopy and imaging techniques like arteriography. Definitive therapy might include surgical intervention, endoscopic therapeutic procedures like laser photocoagulation, variceal banding or injection of gastroesophageal varices by sclerosing agents, selective embolization of bleeding vessels, or mechanical balloon tamponade of bleeding varices.

Intravenous hydrocortisone is mandatory and lifesaving in hypovolemic shock of adrenocortical insufficiency. Hypovolemic shock in diabetic ketoacidosis cannot be fully reversed without the use of insulin.

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CHAPTER 15

Cardiogenic Shock

INTRODUCTION

Cardiogenic shock (CS) is due to a failure of the pumping action of the heart (pump failure), resulting in a lowered cardiac output (CO) and an inadequate tissue perfusion. Progressive tissue hypoxia ultimately leads to irreversible shock and death. CS occurs in approximately 5–8% of patients hospitalized for ST elevation myocardial infarction (STEMI).[1] Left ventricular (LV) infarction is a far more frequent cause of CS compared to right ventricular infarction. Current research[1] shows that though shock is initiated by an impaired CO, neurohormonal factors, changes in the peripheral vascular system and elaboration of increased cytokines causing a systemic inflammatory response syndrome also play an important role in the perpetuation of shock. Early revascularization (ERV) has now been shown to significantly improve survival. More importantly, survivors have a good chance of long-term survival and can enjoy a good quality of life.

ETIOLOGY

Myocardial infarction (MI) with LV failure is the commonest cause of CS. It is important to exclude mechanical complications that can induce shock in patients with MI. These include ventricular septal rupture, contained free wall rupture, rupture of a papillary muscle. Mechanical complications should always be suspected in patients with CS with infarction not involving the anterior wall, particularly when it is a first MI.[1] Infection, bowel ischemia, an occult bleed may complicate MI. Diagnosis can only be made if there is a high degree of suspicion.

Any pathology which causes severe LV dysfunction or failure can cause CS. Acute mitral or aortic regurgitation typically caused by endocarditis or chordal rupture can cause CS. Very critical tight mitral stenosis as also very critical aortic stenosis can present with the clinical features of CS.

Acute myocarditis, congestive cardiomyopathy, hypertrophic obstructive cardiomyopathy may all present with ST elevation, raised cardiac enzymes and shock in the absence of coronary disease. Stress induced cardiomyopathy also called Takotsubo cardiomyopathy is characterized by acute LV dysfunction occurring after emotional stress or respiratory distress; it leads to CS in 4–5% of cases.[2] It is characterized by apical hypokinesia (leading to apical ballooning) and basal myocardial hyperkinesia and can lead to elevated ST segments, raised cardiac enzymes and in a small minority of patients to CS. Aortic dissection can lead to CS either by causing aortic incompetence or MI.

The picture of CS can also be observed in severe tachyarrhythmias, with poor myocardial preservation and myocardial dysfunction following open-heart surgery, massive pulmonary embolism and cardiac compression resulting in low output with shock. These are considered separately though the clinical picture may be indistinguishable from CS. The important causes of CS are listed in Box 1.

INCIDENCE AND RISK FACTORS

Cardiogenic shock complicates 5–8% of patients hospitalized for a STEMI[3,4] and 2.5% of non-STEMI.[5] In the West, there appears to be a decline in the incidence of CS, probably related to the increasing rates of primary percutaneous coronary intervention (PCI) in patients with MI.[6] Early reperfusion therapy in MI should reduce the incidence of CS. A randomized trial of in-ambulance thrombolysis versus primary PCI found no CS among patients assigned to prehospital thrombolysis.[6]

Box 1: Important causes of cardiogenic shock

- Acute myocardial infarction (commonest cause)
- Acute myocarditis
- Congestive cardiomyopathy—
  - Hypertrophic cardiomyopathy
  - Takotsubo cardiomyopathy
- Mechanical causes impairing myocardial function and contractility—
  - Critical aortic stenosis
  - Severe mitral and aortic valvular incompetence
  - Ruptured interventricular septum/ruptured free wall of ventricle/ruptured papillary muscle/ruptured chordae tendinae
- Severe tachyarrhythmias or bradyarrhythmias
- Patients with myocardial dysfunction following open heart surgery
- Myocardial contusion following trauma

Among PCI assigned patients 0.5% developed CS in the group randomized less than 2 hours after MI.

Risk factors for CS in patients with MI include older age diabetes, hypertension, anterior MI, STEMI, hypertension, left bundle branch block, multivessel coronary artery disease, prior MI and a prior diagnosis of heart failure.

PATHOPHYSIOLOGY

A low CO due to the various causes listed above is the primary reason for CS. However, other parts of the circulatory system also become deranged, contributing to the state of shock. Therefore, though the initiating factor is poor pump function, CS is the result of a temporary or permanent derangement of the entire circulatory system.

The onset and severity of shock are often but not always related to the quantitative damage and loss of functional myocardium. An infarction involving more than 40% of the wall of the left ventricle (as could happen following a block in the proximal left anterior descending artery) invariably spells fatal CS. Shock results from death of cardiac muscle leading to poor ventricular contractility and a low CO. There are several contributing factors which potentiate the low output state. These include poor contractility of ischemic muscle surrounding the infarcted zone, an early increase in the compliance of the infarcted area which bulges during systole, a dyssynergy of contraction in the peri-infarcted area and

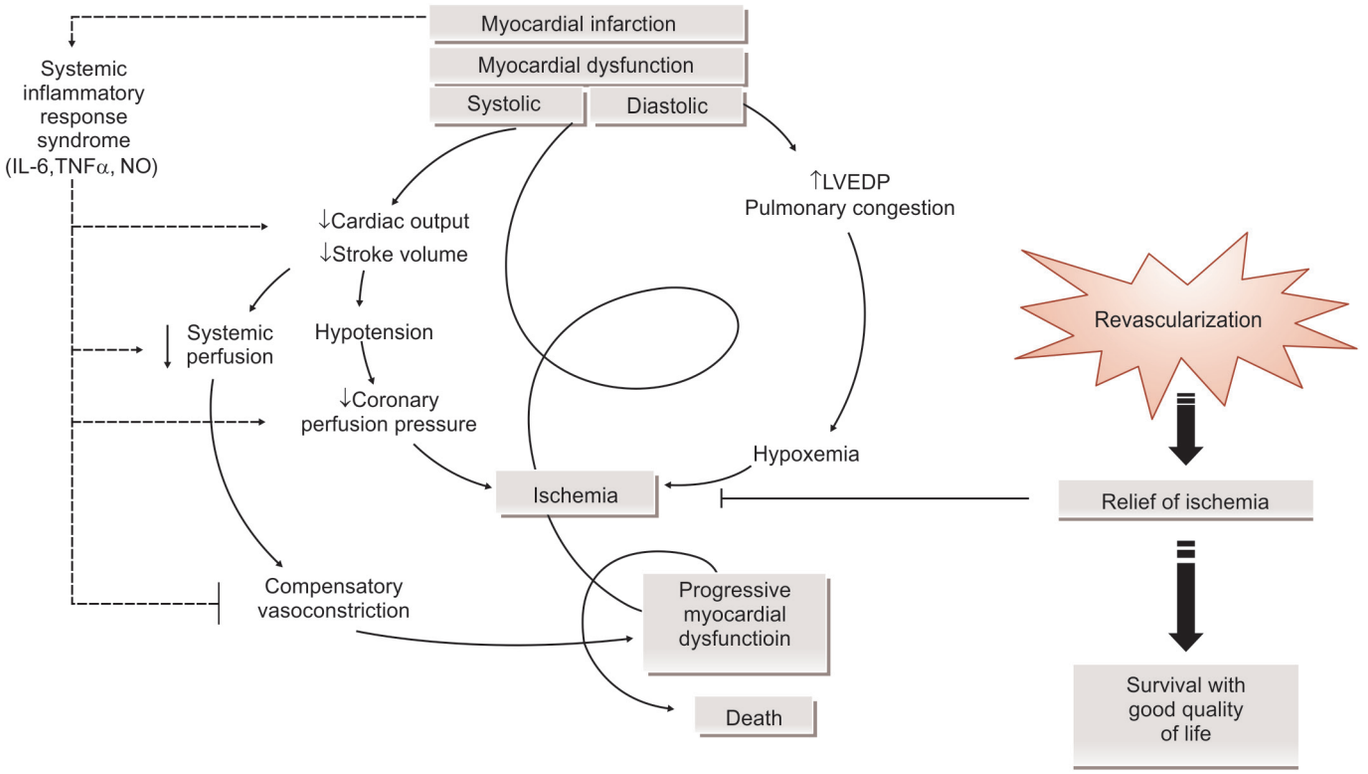


Fig. 1: Current concept of the pathophysiology of CS. The classic description of the pathogenesis is shown in black. Myocardial injury causes systolic and diastolic dysfunction. A decrease in CO leads to a decrease in systemic and coronary perfusion. This exacerbates ischemia and causes cell death in the infarct border zone and the remote zone of myocardium. Inadequate systemic perfusion triggers reflex vasoconstriction, which is usually insufficient. Systemic inflammation may play a role in limiting the peripheral vascular compensatory response and may contribute to myocardial dysfunction. Whether inflammation plays a causal role or is only an epiphenomenon remains unclear. Revascularization leads to relief of ischemia. It has not been possible to demonstrate an increase in CO or LVEF as the mechanism of benefit of revascularization; however, revascularization does significantly increase the likelihood of survival with good quality of life. IL-6 indicates interleukin-6; TNF-α, tumor necrosis factor-α; and LVEDP, LV end-diastolic pressure. Adapted from Hochman and Hollenberg et al. with permission of the publishers. Copyright© 2003, the American Heart Association, and copyright 1999©, the American College of Physicians

metabolic derangements not only within the infarcted region but in the myocardium at a distance from the infarcted zone.[7] As depicted in Figure 1, a diminished CO further diminishes coronary flow causing further ischemia and myocardial damage, with a possible further fall in CO and further hypoperfusion to tissues. A vicious cycle and a downward spiral are set into motion causing progressive myocardial dysfunction and increasing tissue hypoxia that leads to death.

Inotropes, vasopressors can improve both CO and tissue perfusion but do not generally break this vicious cycle and interrupt this downward spiral. The use of an intra-aortic balloon pump (IABP) temporarily supports and improves the circulatory state but this does not last and is no definitive therapy. Revascularization with reperfusion of the myocardium either through PCI, or bypass surgery can however, interrupt this vicious cycle and save lives.

The pathophysiology of CS is complex and cannot be solely attributed to myocardial damage following MI. In a number of patients severe impairment of contractility does not lead to shock; conversely the left ventricular ejection fraction (LVEF) in patients with CS may only be moderately depressed.[8] In the "Should We Emergently Revascularize Occluded Coronary Arteries for Cardiogenic Shock" (SHOCK) trial the mean LVEF was about 30% and the distribution of LVEF in patients in this trial overlaps with that of patients in many post MI trials who had low ejection fraction (EF) with or without heart failure and who were generally ambulatory out-patients.[9-11]

It therefore appears that the magnitude of myocardial damage in CS need not always be profound. However, among patients in shock, LVEF is an indicator of prognosis, the lower the EF, the worse the prognosis.[12] Interestingly, half of CS patients are noted to have small or normal LV size.[12,13] This shows that in these patients there is an absence of the adaptive mechanism allowing acute dilatation, which would have helped maintain a larger stroke volume in the early phase of MI. Systolic function is easy to assess (through echocardiography). Diastolic function is however not easily determined. It is probable that diastolic dysfunction brought about by a fall in ventricular compliance and by abnormalities in ventricular relaxation may contribute to CS in a number of patients.

Cardiogenic shock due to right ventricular infarction and dysfunction occurs in just about 5% of patients with CS due to MI.[14] Severe right ventricular failure results in a decreased right ventricular output (due to poor systolic function) and thereby sharply reduces LV filling and output. The marked increase in the right ventricular end-diastolic pressure (often >20 mm Hg) observed in these patients shifts the interventricular septum toward the LV cavity; this restricts LV filling and also raises left atrial pressure. The generally accepted practice of using a volume load in patients with severe right ventricular dysfunction, so as to maintain an adequate CO and an adequate LV preload may further increase right ventricular diastolic pressure. A marked rise in right ventricular end diastolic pressure caused by a volume load can be potentially harmful as it may worsen hemodynamic changes stated above. Inotropic support is indicated in these patients. An optimal right ventricular end-diastolic pressure of 10–15 mm Hg has been noted to be associated with a higher CO than end-diastolic pressures above or below this level.[15] There is however a fair degree of variability observed with regard to the relation between right ventricular end-diastolic pressure and CO in patients with CS due to right ventricular infarction. It is therefore best for filling pressures to be tailored to optimal CO in each patient.

Shock due to right ventricular dysfunction carries the same mortality as that due to LV dysfunction. In the SHOCK trial the benefit observed following revascularization was similar in patients with right ventricular dysfunction as with LV dysfunction.[9]

Role of Neurohormonal Factors and Systemic Inflammatory Response Syndrome in Cardiogenic Shock

Hypoperfusion due to a low CO triggers the release of catecholamines which constrict peripheral arterioles to maintain perfusion to vital organs. Vasopressin, angiotensin II improve coronary circulation and tissue perfusion, yet cause a significant increase in afterload with further impairment of ventricular dysfunction. Activation of the renin angiotensin system promotes salt and water retention that helps to improve perfusion and yet contributes to pulmonary edema.

Systemic Inflammatory Response Syndrome in Myocardial Infarction and Cardiogenic Shock

Myocardial infarction particularly when associated with CS can cause the SIRS. In spite of compensatory neurohormonal mechanisms, the systemic vascular resistance (SVR) is not always raised in CS. The variable SVR suggests that compensatory neurohormonal mechanisms are not always fully effective. In the SHOCK trial[16] the median SVR in CS was observed to be in the normal range, despite vasopressor therapy. In some patients the SVR is low, similar to septic shock. In fact culture positive bacterial infection develops in a number of patient with a low SVR.[16] These findings suggest the SIRS may play an important role in the pathophysiology of CS and that inappropriate vasodilatation as part of SIRS could result in impaired perfusion of the gastrointestinal (GI) tract, resulting in transmigration of bacteria and sepsis.[17] SIRS occurs more frequently with increased duration of shock.[17,18] Cytokine levels including interleukin-6 and tumor necrosis factor are noted to be elevated. Both these cytokines have a myocardial depressant action; tumor necrosis factor also induces endothelial dysfunction further impairing coronary flow. C reactive protein, procalcitonin, neopterin and other circulatory factors also perhaps contribute to SIRS.[1]

Excess nitric oxide (NO) may also contribute to SIRS. MI is associated with an increase in NO synthase.[1] The latter leads to an excess of NO which causes vasodilatation, myocardial depression and counters the effects of catecholamines. However, NO synthase inhibitors in a multicenter trial did not improve hemodynamics and outcome in CS.

Mechanical Factors

There are specific hemodynamic complications other than the loss of viable myocardium that can precipitate or worsen shock in MI. These include a ruptured interventricular septum, ruptured free wall of the ventricle or a ruptured papillary muscle.

Iatrogenic and Treatable Factors

There are some iatrogenic and/or treatable factors that can potentiate CS. These include—

- Hypovolemia due to the use of diuretics, sweating, restricted fluid intake and vomiting. Blood loss due to undetected bowel ischemia could also cause hypovolemia.
- Tachyarrhythmias or bradyarrhythmias.
- Depressant action of drugs. The use of propranolol in the setting of an evolving severe pump failure can be particularly disastrous. Depressant drugs may far outlast the biological half-life of the agent, since a positive feedback mechanism during the use of the drug may become self-perpetuating even when the drug is withdrawn. Over-sedation with narcotics and tranquillizers can also induce hypotension and worsen shock.
- Metabolic acidosis and electrolyte disturbances potentiate myocardial dysfunction.
- Unrelieved hypoxia.
- Severe prolonged unrelieved pain may worsen the shock state.
- Sepsis may complicate CS; it should be suspected in the presence of a low SVR. Blood cultures may be positive.
- Diuretics (particularly high doses) may cause or contribute to shock in patients with MI by diminishing circulatory volume.
- Pulmonary embolism.
- Excess volume loading in patients with right ventricular infarction can also contribute to shock.

Factors aggravating shock in acute MI are given in Box 2.

In summary, the pathophysiology of CS is initiated by pump failure but then involves other parts of the circulatory system. Compensatory neurohormonal mechanisms are often inadequate to counter CS. The SIRS has been shown to play an important role in the pathophysiology of CS. Finally, other factors, some treatable and some iatrogenic may contribute to CS.

Box 2: Factors aggravating cardiogenic shock in acute myocardial infarction

- Severe unrelieved pain
- Hypovolemia
- Tachyarrhythmias or bradyarrhythmias
- Depressant action of drugs, e.g. propranolol, overuse of narcotics and sedatives
- Metabolic acidosis and electrolyte disturbances
- Unrelieved hypoxia
- Pulmonary embolism
- Sepsis
- Diuretics in large doses
- Excess volume loading in patients with right ventricular infarction

CLINICAL FEATURES

The features of shock develop against the background of acute MI, or against the background of other severe low output states due to myocardial dysfunction, or to mechanical problems (as in severe valvular heart disease).

At least two of the five features listed below are present—

1. Hypotension with a systolic pressure below 90 mm Hg or a mean arterial pressure less than 55 mm Hg. There are a few points worthy of note in relation to hypotension. Blood pressure readings taken by the cuff method are unreliable in the presence of severe vasoconstriction. They are often much lower and often unobtainable by the cuff method under the above circumstances, even though pressure measurements via an intra-arterial cannula show satisfactory readings. It is equally important to remember that shock can exist with a systolic pressure higher than 90 mm Hg, particularly in the presence of compensatory vasoconstriction which raises the peripheral vascular resistance. Also, a patient may at times remain well perfused with a systolic blood pressure between 70 and 90 mm Hg. Tachycardia is frequently associated with hypotension but shock can exist with a bradyrhythm, or even with a normal heart rate.
2. Cold, pale, clammy or sweaty skin. The skin over the peripheries, forehead, nose, lips, face, first turns cold and clammy; the coldness then extends to the trunk.
3. A fall in urine output to less than 25 mL/hour with a sodium content less than 30 mEq/L.
4. Impaired cerebration—anxiety, restlessness, agitation, confusion and later, obtundation.
5. Metabolic acidosis due to lactic acid accumulation.

When life support systems keep a patient in severe CS alive for a few days, signs of increasing multiple organ dysfunctions are observed.

DIAGNOSIS[1]

The diagnosis of CS is evident when it evolves against the clinical features, electrocardiograph (ECG) and serial enzyme changes of an MI. When shock follows very soon after an MI, or if for any reason the history is unavailable, or the ECG changes are atypical, the diagnosis is more difficult. A patient in severe shock may never complain of chest pain pointing to an underlying MI, and yet a patient with hypovolemic shock due to a massive GI bleed may complain of ischemic cardiac pain and thus mislead the clinician into arriving at a wrong diagnosis.

The diagnosis of CS due to low-output states related to cardiomyopathy and severe valvular heart disease should be

evident on a clinical examination and relevant investigations. An etiology which is often missed is the low-output state due to a very tight aortic stenosis. The typical murmur may be absent in these patients because of the sharp reduction in the forward flow. An echocardiography is mandatory in all patients, and should aid in making a convincing diagnosis of aortic stenosis under the above circumstances. Acute aortic incompetence as a cause of a low-output state, may also be missed as the aortic diastolic murmur is short (due to high left ventricular end-diastolic pressures), and the left ventricle is not enlarged. The diagnosis is confirmed by echocardiography, and by catheter studies on the heart.

Cardiogenic shock can be mistaken for—

1. *Shock due to a severe internal bleed* A common site for an internal bleed is the GI tract. The bleed may not be evident for some hours, and blood loss for the first 6–12 hours is not manifested by an appreciable fall in the hemoglobin or the hematocrit. The diagnosis is particularly difficult when a large occult bleed in an elderly individual causes prolonged ischemic cardiac pain with ST-T changes in the ECG. The diagnosis is however obvious when there is malena or there is massive bleeding from the rectum or when the gastric aspirate through the nasogastric tube contains blood. A ruptured aortic aneurysm can also produce a rapidly evolving hypovolemic shock that may be mistaken for CS. A clinical examination however will always reveal collapsed neck veins in the former. Quick investigations should localize the source of bleeding. In difficult cases, a hemodynamic profile [low central venous pressure (CVP) and low pulmonary capillary wedge pressure (PCWP)] obtained through a Swan-Ganz catheter can confirm hypovolemia as the cause of shock.
2. *Massive pulmonary embolism* It produces the picture of CS. The ECG may simulate a myocardial infarct because of evidence of subendocardial injury. A S1Q3 pattern, right bundle branch block, a right ventricular strain pattern with a P pulmonale and clockwise rotation should point to a correct diagnosis. Pressure readings show a raised CVP, a high pulmonary artery (PA) end-diastolic pressure and a low to normal PCWP.
3. *Dissecting aneurysm of the aorta* A dissection of the thoracic aorta can result in pain indistinguishable from an acute MI and a picture of rapidly evolving shock. A suspicion of this diagnosis is aroused when the patient complains of excruciating pain chiefly in the back, and the ECG does not reveal the typical changes of infarction. An echocardiogram would help in the diagnosis; a computed tomography (CT) or magnetic resonance imaging (MRI) of the chest is a confirmatory test.
4. *Cardiac tamponade* It is characterized by an increasing heart rate, a rising CVP and a falling blood pressure. A PA catheter reveals an equilibration in the mean right atrial, PA diastolic and PCWPs.
5. Other conditions which mimic CS are hypotension following drugs, and septic shock, where the source of sepsis is not evident, and where there is an associated severe myocardial dysfunction. Shock following acute fulminant pancreatitis can also mimic CS, especially when the former is associated with grossly abnormal ST segment changes in the ECG. A full clinical examination and an evaluation of basic investigations point to the correct diagnosis.

The emphasis in the diagnosis of CS should be on the early recognition of signs of reduced tissue perfusion. Thus a patient with MI who has an unexplained change in the pulse rate, pulse volume, blood pressure, urine output or skin temperature is suspect as being in preshock, even though the clinical features do not fulfill the criteria listed above.

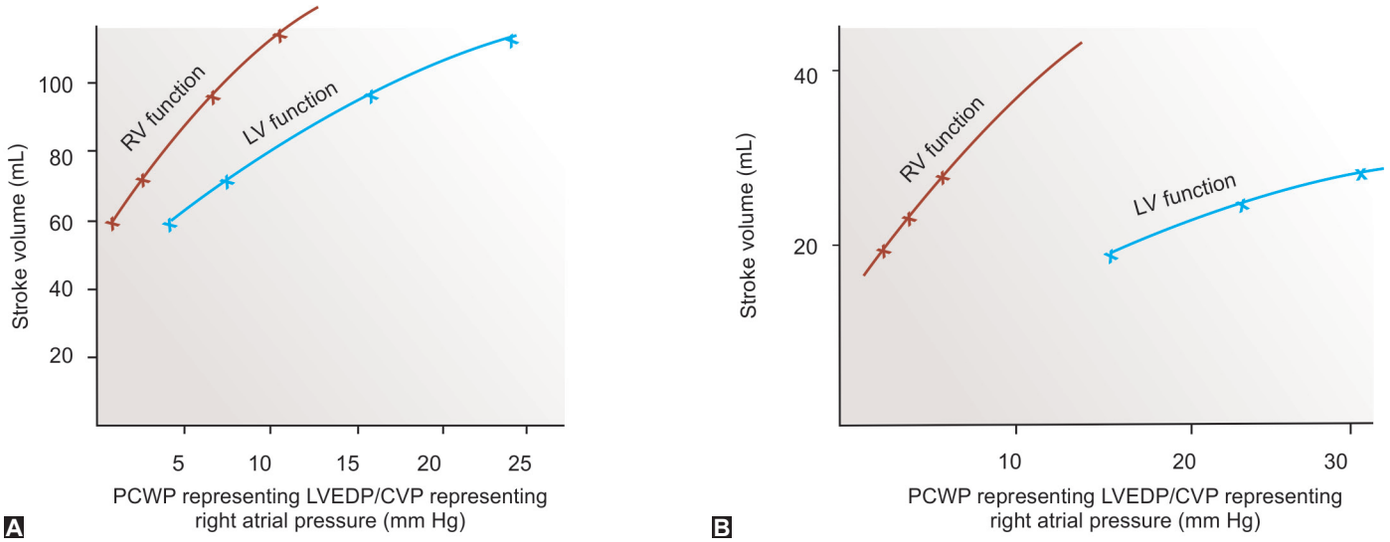
HEMODYNAMIC CHANGES AND HEMODYNAMIC PROFILE

A failure of pump function is followed by a failure of forward flow, resulting in poor perfusion and poor tissue oxygenation. This is the essence of CS. A failure of pump function of the left ventricle is also associated with increased LV end-diastolic pressure, increased left atrial pressure and increased PCWP. When the latter clearly exceeds the oncotic pressure exerted by the plasma proteins, pulmonary edema results. The picture of CS as has been explained below is associated with the following hemodynamic effects and profiles.

Hypoperfusion and Pulmonary Edema

Varying degrees of hypoperfusion ranging from moderate to very severe with varying degrees of pulmonary edema ranging from moderate to fulminant are observed (Figs 2A and B). The severest form of this situation is exemplified by a patient who is pulseless, pressureless, anuric, hypothermic with lactic acid acidosis and with evidence of failure of other vital organs due to very poor forward flow and perfusion; fulminant pulmonary edema is simultaneously present. Death in such instances is inevitable. However, as explained, varying gradations in both tissue hypoperfusion and in the degree of pulmonary edema are encountered. The hemodynamic profile shows the following—

- Normal or elevated CVP.
- Increase in PCWP greater than 18 mm Hg—the greater the rise in PCWP, the greater the degree of pulmonary edema. Fulminant edema is generally associated with a PCWP approaching or exceeding 30 mm Hg.
- A lowered CI less than 2.5 L/min/m^2—the lower the CI, the poorer the tissue perfusion. In very severe cases, the CI is less than 1.8 L/min/m^2 and terminally may even approach 1 L/min/m^2. In patients with early CS, the CI may only be slightly less than normal because of compensatory mechanisms.
- A systolic blood pressure often less than 90 mm Hg. In early or evolving shock, the blood pressure may be maintained at or above 100 mm Hg because of a raised SVR. In severe



Figs 2A and B: (A) Normal right and left ventricular function curves in a healthy volunteer as plotted by stroke volume against PCWP/CVP; (B) Right and left ventricular function curves in a patient with cardiogenic shock due to massive anterior wall infarction. Note (i) the wide separation of the RV and LV function curves resulting in a susceptibility to pulmonary edema; (ii) the marked flattening in the LV function curve resulting in poor forward flow with poor tissue perfusion and shock

shock with failure of forward flow, the systolic blood pressure is less than 70 mm Hg.

- A raised SVR—this is a compensatory mechanism to keep the blood pressure close to normal.

Isolated Hypoperfusion

It is very important to realize that pump failure should not necessarily be equated solely to increasing PCWP and pulmonary edema. In fact, pump failure may be solely characterized by poor flow of blood in the forward direction from the left ventricle causing severe shock, without a rise in the PCWP to an extent that leads to pulmonary edema. This was beautifully illustrated by Bradley, in his excellent small book on Studies in Acute Heart Failure.[19] Bradley showed through his hemodynamic studies, that when right ventricular function curves (representing stroke volume equations) were severely depressed and shifted to the right so that they overlapped the LV function curves, the lungs were protected from pulmonary edema, even though the patient was in shock. We were subsequently able to demonstrate this on our patients as well. The stroke volume equations of the right and left ventricles in these patients are illustrated in Figure 3.

The hemodynamic profile in patients with shock due to isolated hypoperfusion is as follows—

- Increase in mean atrial pressure or CVP.
- PCWP less than or equal to 15 mm Hg.
- Low CI less than 2.2 L/min/m^2 and often below 1.8 L/min/m^2.
- Hypotension with systolic BP less than 70–90 mm Hg.
- Increase in SVR.

The above hemodynamic effects and profile can be brought about in the following conditions—

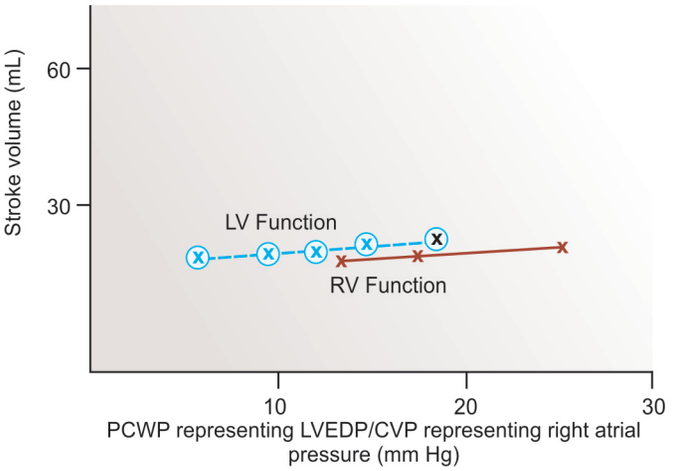


Fig. 3: Right and left ventricular function curves in a patient with myocardial infarction and cardiogenic shock with extremely poor perfusion and shock but no pulmonary edema. Note (i) The flattening of both right and left ventricular function curves resulting in poor perfusion and shock; (ii) The right ventricular function curve overlaps, and is below and to the right of the left ventricular function curve, in contrast to the normal curves. The relation between right and left atrial pressure is such that the patient is protected from pulmonary edema. This is observed in a global infarct (right and left ventricular wall involved), and in a massive anterior wall (LV) infarct with severely depressed right ventricular function

- A global infarct when the LV wall as well as the right ventricle are both infarcted and the right ventricular function curve is even below the LV function curve.
- An infarct of the LV wall where the overall pump function of not only the left ventricle but also of the right ventricle is grossly disturbed. This occurrence stresses the importance

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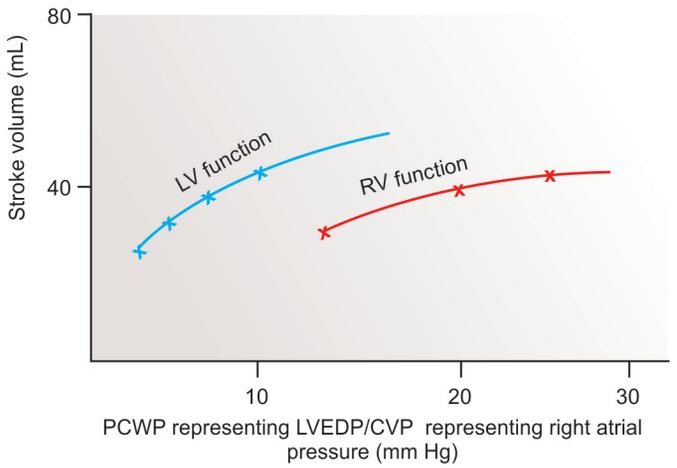

Fig. 4: Right and left ventricular function curves in a patient with inferior wall infarction and cardiogenic shock, but no pulmonary edema. Note right ventricular function curve is flattened and transposed below and to the right of the left ventricular function curve. Relation between right and left artial pressures is such that the patient is protected from pulmonary edema

of not always considering the heart to be consisting of two separate pumps (the right and the left), but as an overall, single, interdependent functioning unit so that gross disturbance in the left side can also affect the function of the right heart. Perhaps this is because of the septal wall which is common to the left and right ventricles; poor function consequent to a massive septal infarct would affect both ventricles. A further contributory factor is that even though the left ventricle may be infarcted, right ventricular function may be seriously prejudiced because of overall global ischemia. This is generally related to critical narrowing of the right coronary artery with poor collateral flow from the branches of a blocked left anterior descending artery to the right coronary vessels, and also to a falling aortic pressure leading to a poor circulation through the right coronary artery.

- In pure severe right ventricular infarction, the hemodynamic profile shows a marked increase in the CVP or in the mean right atrial pressure, a normal or low PCWP, a marked fall in the CI to less than 2 L/min/m^2, and severe hypotension with a rise in the SVR (Fig. 4).

Hypovolemia and Pump Failure

The association of hypovolemia with pump failure also adds a new dimension to the hemodynamic profile of pump failure. Typically hypovolemia in these patients as stated earlier, results from a combination of vomiting, very poor fluid intake or the use of diuretics. It could also be due to blood loss from a complicating bowel infarction.

The hemodynamic profile shows—

- A lowered CVP.
- A PCWP less than or equal to 15 mm Hg.
- Lowered CI of less than 2.5 or even less than 2.2 L/min/m^2.
- Hypotension, systolic pressure less than or equal to 90 mm Hg with an increased SVR.

A volume load enough to raise the PCWP greater than or equal to 18 mm Hg raises the CI significantly, yet the degree of rise is far less than what would be expected with normal pump function.

In fact poor pump function becomes unmasked when the volume load raises the PCWP to 15–18 mm Hg.

Special Hemodynamic Profiles

Complications of MI like a ruptured ventricular septum or a ruptured papillary muscle produce distinct hemodynamic profiles. Thus a ruptured ventricular septum is associated with—

- Rise in CVP and right atrial pressure.
- Rise in pulmonary systolic and diastolic pressures.
- A rise in PCWP greater than 18 mm Hg to often as high as 30 mm Hg.
- Fall in CI less than 2.2 L/min/m^2.
- Arterialization of blood sampled from the right ventricle and PA (i.e. a marked step-up of O_2 saturation of blood from the right ventricle and PA compared to blood in the superior vena cava or right atrium).

Papillary muscle dysfunction will show a high PCWP, a low CI, hypotension and prominent "v" waves with characteristic morphology in pressure tracings obtained from the PA and PA occlusive sites.

Various hemodynamic profiles described above are detailed in Table 1.

Treatment (Box 3)

Currently, the management of CS in acute MI is to improve the patient's hemodynamic profile so that prompt diagnostic testing and intervention, whenever possible, either through percutaneous intervention (percutaneous angioplasty and stenting) or in carefully selected cases through bypass surgery become feasible. Improvement in the hemodynamic profile and the general circulatory state is brought about by the immediate use of medical measures outlined in this section, and by using the support of the Intra Aortic Balloon Counterpulsation (IABP). The latter assist device should be used early and not late in the management of severe CS. In fact, in patients admitted to the intensive care unit (ICU) with severe CS, aortic balloon pump support must be used promptly, *pari passu* with other medical treatment outlined below. The above policy is only possible in an ideal set-up which has trained medical and paramedical personnel, good monitoring facilities, an intra-aortic balloon support and an infrastructure that provides for diagnostic angiography, PCI and coronary artery bypass surgery if so required, promptly or very soon after a patient's admission. There are perhaps very few centers in India and other developing countries which provide this perfect set-up. Yet as is explained later in this

Table 1: Hemodynamic (HD) profiles in cardiogenic shock

HD Profiles	*CVP (mm Hg)*	*SBP (mm Hg)*	*CI (L/min/m²)*	*PCWP (mm Hg)*	*SVR (dynes-sec/cm⁵)*
Hypoperfusion with pulmonary edema	Normal or↑	<90	< 2.2	20–30 or more	↑ to ↑↑↑
Isolated hypoperfusion (global infarct)	↑ or ↑↑	<70–90	< 2.2	≤15	↑ to ↑↑↑
Hypoperfusion with severe right ventricular infarction	↑↑	<70–90	< 2.2	<15	↑ to ↑↑↑
Hypovolemia with pump failure	Normal or low	<90	< 2.2	≤15	↑ to ↑↑↑
Ruptured ventricular septum or papillary muscle	↑↑	<90	< 2.2	>15; may be 20–30	↑ to ↑↑↑

Abbreviations: HD, hemodynamic; CVP, central venous pressure; SBP, systolic blood pressure; CI, cardiac input; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

Box 3: Principles of management in cardiogenic shock

Objective

Improve hemodynamic profile to an acceptable state, through pharmacological measures + use of IABP so that diagnostic testing and intervention, whenever possible through angioplasty, or through surgery, become feasible

Pharmacological measures to improve hemodynamics—

a. Maximizing preload: Volume challenge if PCWP is less than 15 mm Hg—
   - Increase PCWP to 18–20 mm Hg or even more provided there is no pulmonary edema

b. Use of vasodilators—IV nitroglycerin in patients with high PCWP and well-marked pulmonary edema (reduce PCWP to 15–18 mm Hg)

c. Increasing cardiac contractility—
   - Dobutamine or dopamine by IV infusion or both
   - Digoxin; other inotropes in rare instances

d. Judiciously combine a, b and c

e. Use of noradrenaline if hypotension persists in spite of use of dopamine (>10 ug/kg/min)

f. IV furosemide combined with b and c if there is pulmonary edema

g. Maintain oxygenation—administer oxygen at flow rate of 6–8 L/min. If PaO_2 still less than 60 mm Hg, or if respiratory distress (rate >35/min), intubate and put on ventilator support

h. Correction of electrolyte and acid-base abnormalities

i. Correction of factors aggravating cardiogenic shock

Abbreviations: PCWP, pulmonary capillary wedge pressure; IABP, intra-aortic balloon pump; IV, intravenous.

section, though mortality increases as time to revascularize increases, *there is a survival benefit following revascularization as long as 48 hours after MI and 18 hours after the onset of CS.*[20]

Where facilities for interventional revascularization are unavailable or too delayed, pharmacological measures together with an intra-aortic balloon support offer the only chance for survival. Hemodynamic management through pharmacological measures instituted at the time of admission continues through interventional therapy, and well after, till recovery ensues.

This section first deals with monitoring procedures in CS, then with management of CS with emphasis on pharmacological measures complemented by the use of IABP device to help restore hemodynamic stability. It goes on to discuss reperfusion and revascularization in CS and the evidence to show that the earlier the reperfusion through interventional procedures, the better the outcome. There follows a brief description of ventricular assist devices and the management of CS due to mechanical complications following MI. The section ends with a brief description on long-term survival and quality of life after surviving CS.

MONITORING THE PATIENT IN CARDIOGENIC SHOCK[1]

Half-hourly pulse, and two to four hourly skin and rectal temperature, as well as hourly urine output through an indwelling Foley's catheter should be charted. The blood pressure may need to be checked very frequently and in patients with clinical evidence of peripheral vasoconstriction, it is important to cannulate the radial artery and connect the cannula or catheter to a pressure monitor so that correct pressure readings are obtained and recorded. The ECG is continuously monitored. The blood count, packed cell volume (PCV), serum electrolytes, blood urea, non protein nitrogen (NPN), creatinine, blood lactate levels, other blood chemistry, arterial pH and arterial blood gases are done on admission and repeated as and when necessary. A chest X-ray is mandatory, and follow-up X-rays are done to check in particular for radiological evidence of pulmonary edema. Both the CVP and the oxygen saturation of blood in the superior vena cava ($ScvO_2$) are continuously monitored through a central venous catheter; arterial oxygen saturation is also continuously monitored. In a number of patients detailed hemodynamic monitoring (often through the use of

Box 4: Monitoring patients in cardiogenic shock

- Half-hourly heart rate, blood pressure and respiratory rate
- Hourly skin and rectal temperature; clinical monitoring
- Hourly urine output through indwelling catheter
- Continuous ECG monitoring
- Blood count, serum biochemistry, arterial pH and arterial blood gases done on admission and repeated as and when necessary
- Chest X-ray
- Hemodynamic monitoring—
  - Central venous pressure
  - Pulmonary artery pressures—pulmonary artery end-diastolic pressure, pulmonary capillary wedge pressure
  - Cardiac output, cardiac index, stroke volume index, systemic vascular resistance, left and right ventricular stroke work indices
  - DO_2, $\dot{V}O_2$

PA catheter) is helpful (Box 4). Hemodynamic measurements should be done only by intensivists who are experienced both in noting correct measurements and in the assessment of values obtained.

Clinical monitoring is extremely important with particular reference to all signs of shock (see Clinical Features). These should include respiration, pulse volume and rate, CVP, mental state, respiratory rate and the degree of pulmonary congestion as judged by crackles on auscultation and by assessment of serial chest X-rays.

Central Venous Pressure

It is important to learn to gauge CVP on clinical examination. In fact, one should easily recognize a raised or normal jugular venous pressure (JVP); with a little practice one should also detect a low JVP. But for an accurate measurement of the CVP, a central venous line connected to a pressure monitor is necessary. If a pressure monitor is unavailable, the central line is connected through a bivalve to a water manometer. The zero level measurement is in the plane of the mid-axillary line, midway between the sternum and the back. Many units in the country cannot afford the use of PA catheters with the gadgetry to measure right-sided pressures, PCWP and CO; but a central venous line can be easily arranged with a bare minimum of facilities.

Left Ventricular Filling Pressure

The preload is ideally determined by measuring the end-diastolic volume. This is difficult in an ICU setting in a patient with MI. A practical method of gauging the preload is by measuring the PA end-diastolic pressure, which in MI approximates the pulmonary occlusive or the PCWP. The latter in turn, corresponds reasonably with the LV filling pressure. The compliance of the ventricular wall in MI may be decreased so that the relation between the filling pressure and the end-diastolic volume is altered (see Chapter Overview of Shock Syndromes). Even so, measurement of the PA diastolic pressure or the PCWP remains the most readily available method of gauging preload in these patients. Serial measurements are of greater value than isolated readings. It is important to stress that the CVP cannot be relied upon to give an idea of the LV filling pressure in CS. The CVP may in fact be perfectly normal in some patients even though the left ventricular filling pressures are markedly raised.

Cardiac Output

Ideally all patients with CS should have their CO measured and monitored. Serial measurements of CO are made through the Swan-Ganz (S-G) catheter using the thermodilution technique. Samples of mixed venous blood from the PA are also serially obtained through the S-G catheter. A lowered pressure of mixed venous oxygen (PvO_2) or a lowered mixed venous oxygen saturation ($S\dot{v}O_2$) points to a lowered CO. Serial values of $ScvO_2$ help to indicate the trend in changing CO (see Chapter Hypovolemic and Hemorrhagic Shock). Filling pressures of the left ventricle, CO, SVR, stroke volume, stroke work, are often measured through a PA catheter or S-G catheter. The use of the PA catheter has declined significantly following a prospective observational study that its use was associated with a poor outcome.[21] However, no such association has been shown in CS.[22] Many units continue to use the PA catheter in CS with severe hypotension. Clinical echocardiography is a reasonable alternative as both PA systolic and wedge pressure can be accurately measured by this modality. In particular, the finding of a short mitral decelerating time is highly predictive of PCWP greater than 20 mm Hg in CS.[23]

There are comparatively few centers in developing countries including India, that can afford the luxury of measuring CO. When facilities are lacking, changes in the CO should be clinically gauged by observing changes in tissue perfusion, blood pressure, urine output and changes in the function of other vital organs. Clinical examination and chest radiographs help in roughly assessing PCWP in about 70% of patients with CS.

Management[1]

General Measures

Antithrombotic therapy with aspirin and heparin should be given in patients with CS as is routinely recommended for MI. Clopidogrel is indicated in all patients who undergo PCI. The patient is given high flow oxygen, is closely monitored, while at the same time preparations are made to promptly insert an intra-aortic balloon counterpulsation device (IABP) in all hypotensive patients. Blood sugars are brought under tight control (<140 mg/dL) with the use of insulin.

Pharmacological Treatment to Restore Hemodynamic Stability

Increasing CO and improving tissue perfusion This is the basic principle and forms the essence of therapy. Factors which determine CO are—

- End-diastolic fiber length, i.e. end-diastolic volume or preload. Roughly in clinical practice (with the exceptions stated above), this is equated to the filling pressure of the ventricles, which in turn (with regard to the left ventricle) is equated to the measured PA end-diastolic pressure or the measured PCWP.
- Contractility of the ventricular muscles.
- Heart rate and rhythm.
- Afterload. In MI this is clinically related (again roughly) to the outflow resistance offered by the constricted peripheral vessels.

Management should be directed to the skillful manipulation of the factors stated above so that CO and perfusion improve.

Maximizing Preload

It has been shown that the optimal filling pressures of the left ventricle in shock following MI, range between 15–24 mm Hg.[4] If therefore in a hypotensive shocked patient the PCWP is normal to low (< 15 mm Hg), and the CVP is also low or on the lower side of normal, the patient is hypovolemic for some reason and needs a volume load. Boluses of 300 mL of dextrose saline or Ringer Lactate are rapidly infused over 30 minutes till such time as the low blood pressure and other signs of shock improve. One should aim to maintain a pulmonary artery end-diastolic pressure (PAEDP) or PCWP between 18–20 mm Hg. The degree to which CO, blood pressure and signs of shock improve will depend on the underlying myocardial dysfunction. If hypovolemia is a significant contributory factor in shock, then increasing the preload (PCWP or PAEDP) will produce a significant improvement in the CO, blood pressure and the clinical features of shock. If on the other hand, hypovolemia is a minor or incidental finding, then raising the PCWP to 18–20 mm Hg may produce only a slight improvement in the CO and blood pressure, thus unmasking the severity of underlying myocardial dysfunction.

If to start with the PAEDP or the PCWP is less than 20 mm Hg, one may still maximize the preload by judiciously pushing IV fluids so that the PAEDP increases to around 20 mm Hg. The patient should however be under constant clinical and frequent radiological monitoring, to determine increasing crackles within the lungs and increasing radiological evidence of pulmonary edema. Some degree of pulmonary edema may be acceptable if improvement in CO and tissue perfusion is obviously manifest. In our experience in Mumbai, India, in most patients with CS the optimum PAEDP is between 15 and 20 mm Hg, these values being a little lower than those reported from the West. However, the relation of optimal filling pressure to optimal CO should be individualized as this relationship may vary from patient to patient. If during the process of maximizing the preload frank pulmonary edema ensues, the volume challenge is stopped and 40–100 mg IV furosemide administered intravenously.

If an increase in the PAEDP to above 20 mm Hg brings no improvement in either the CO or tissue perfusion (ideally gauged both clinically and by sequential CO measurements), then further management consists of the manipulation of the afterload and cardiac contractility. Also, if to start with the PAEDP is very high (well above 20 mm Hg), volume infusion is pointless and will only add to the existing pulmonary edema, without increasing the CO or tissue perfusion. In such cases, measures to reduce a very high preload to optimal levels, and measures to improve cardiac contractility, should immediately be resorted to. IV furosemide should also be given to decrease preload and reduce pulmonary edema.

Use of Vasodilators

If the hemodynamic profile shows a raised PAEDP (> 18–20 mm Hg), a systolic blood pressure greater than or equal to 90 mm Hg, a lowered cardiac index and systemic hypoperfusion, vasodilator therapy is indicated.

Vasodilators reduce the abnormally high preload and afterload, thereby improving pump function. The fall in peripheral resistance improves CO (as the outflow impedance is significantly reduced), and therefore in many patients there is no significant fall in blood pressure. Even when there is a slight fall in arterial blood pressure, the tissue perfusion may well improve, as judged clinically. Nitrites chiefly reduce the preload and have a much smaller effect on the afterload. With a marked increase in PAEDP and frank pulmonary edema, IV nitroglycerin (0.3–4 µg/kg per minutes) is the drug of choice. The initial dose of nitroglycerin should be 10 µg/minute given through a microdrip. This is gradually increased till the optimal effects are achieved. The end-point here is a PAEDP of about 15–18 mm Hg. The infusion may have to be stopped or sharply reduced if there is a significant reduction in the systolic blood pressure. Tachycardia and severe headache are important side effects of nitroglycerin. Unfortunately, tolerance to nitroglycerin is observed within 24–72 hours. Once the patient's hemodynamic profile has improved, the patient is switched to oral nitrites.

Sodium nitroprusside is no longer used as a vasodilator in CS. It can cause a disastrous crash in the blood pressure even in carefully titrated doses. The drug causes marked arterial vasodilatation at the level of the resistance vessels. This can result in a coronary steal syndrome with further ischemic insult to the already damaged myocardium.[24] Use of sodium nitroprusside can also cause cyanide poisoning with metabolic acidosis. The toxic effect is not as uncommon as was previously thought.

Use of vasodilator therapy is difficult without adequate monitoring facilities—an arterial cannula in the radial artery, an S-G catheter to monitor PAEDP or PCWP, and if possible the CO. It is also imperative to control and monitor the infusion rate if disaster is to be avoided.

Increasing cardiac contractibility When the hemodynamic profile of a patient in CS shows hypotension (systolic BP between 70 and 90 mm Hg or even lower) a reduced CI, a raised PCWP (well >20 mm Hg) with increased SVR and poor tissue perfusion, inotropic drugs must be used to improve

cardiac contractility. As far as possible it is unwise to use inotropic drugs before first determining the CVP and the PAEDP which means that it is wrong to use inotropic drugs without first determining whether volume loading by IV infusion would be helpful or not (except of course in patients who have frank pulmonary edema). Inotropic drugs often produce both central and venous constriction (by increasing venous tone) thereby raising the CVP, and also at times pulmonary venous constriction, thereby raising the PAEDP. A wrong picture of iatrogenically induced high filling pressure may then be obtained after the use of inotropic drugs, and the major therapeutic intervention of increasing effective circulatory volume is CS may not be availed of.

Use of inotropes and vasopressors[25] The inotropic drugs most frequently used to augment cardiac contractility are dopamine and dobutamine.

1. *Dopamine* is perhaps the drug most frequently used to start with. Dopamine combines powerful inotropic properties with vasopressor properties (due to stimulation of alpha receptors) and effectively raises perfusion pressure. It is started with a dose of 5 ug/kg per minute and the dose is progressively increased every 10–15 minutes (to a maximum of 20–30 ug/kg per minute) till the systemic arterial blood pressure rises to acceptable levels (mean arterial blood pressure 65–70 mm Hg) for a reasonable perfusion to the brain and myocardium. Cerebral and renal perfusion necessitate a systolic perfusion pressure of more than 75–80 mm Hg; adequate coronary perfusion necessitates a systemic diastolic pressure of 65 mm Hg with a LV filling pressure of 15 mm Hg. An unfortunate side-effect of dopamine and other inotropes observed in some patients is tachycardia and arrhythmias which prevent the administration of an appropriate dose.

2. *Dobutamine* When hypotension is not marked (between 80 and 100 mm Hg) some units prefer to start with dobutamine given at an infusion rate of 2–15 ug/kg per minute. Dobutamine improves stroke volume, CO and ventricular performance. The overall improvement in ventricular performance and function leads to decreased ventricular filling pressures. Dobutamine increases systolic blood pressure through its effect on the stroke volume and pulse pressure, thereby, improving peripheral tissue perfusion. At the same time it directly reduces ventricular afterload and wall stress by a direct reduction in systemic and pulmonary vascular resistances, ventricular systolic volume and ventricular filling pressures.[26] Dobutamine increases diastolic time (through a reduced systolic time), and increases perfusion pressure through the coronaries thereby leading to increased myocardial oxygen supply, when this is vitally necessary.[26] These effects have been proven in animal experiments and in humans with ischemic heart disease.[26] Dobutamine should be started at an infusion rate of 2–3 µg/kg per minute and the rate progressively increased till the patient improves hemodynamically and remains stable.

A combination of dopamine and dobutamine is often necessary to help improve the hemodynamic state.

If, however, dopamine alone or even a combination of dopamine and dobutamine fail to raise the pressure and improve the hemodynamic state, noradrenaline is added in an IV infusion at the rate of 2–5 µg per minute, slowly increasing the dose to obtain a satisfactory systolic pressure. Both dopamine in a dose greater than 10 ug/kg per minute and noradrenaline are strong vasoconstrictors; large doses of these vasopressors may worsen tissue perfusion and aggravate shock. Large doses can also markedly increase the afterload and thereby further compromise cardiac function. An absent or poor response to inotropes and vasopressors is associated with a mortality greater than 90%. Dopamine in doses greater than 30 ug/kg per minute and noradrenaline in a dose greater than 30 µg per minute are likely to do more harm than good.

3. *Digoxin* is probably of little value in the management of CS except for the control of a rapid ventricular rate resulting from atrial fibrillation. It may also be used when LV failure is chiefly characterized by pulmonary edema rather than by poor tissue perfusion. A dose of 0.25 mg is given intravenously and repeated 6 hourly till a digitalizing dose of 0.75 mg to a maximum of 1 mg is reached.

4. *Other Inotropes* Amrinone is a far weaker inotrope as compared to dopamine or dobutamine. It increases cardiac contractility independently of catechol pathways. It is believed to act by increasing cAMP and calcium concentrations. The increased cAMP in smooth muscles decreases peripheral and pulmonary vascular resistances as also resistance in the coronary circulation. It increases stroke volume without producing a tachycardia. The initial dose is 0.75 mg/kg given over 5 minutes, followed by an infusion of the drug at 5–10 µg/kg per minute. The total daily dose should not exceed 10 mg/kg. A combination of dobutamine plus amrinone is often employed immediately after bypass surgery to counter myocardial depression in patients who to start with have a poor ejection fraction.

Glucagon is an inotrope which increases cardiac contractility and decreases peripheral resistance. The dose is 4–6 mg intravenously in a bolus followed by an infusion of the drug at a rate of 4–12 mg/hour. It could be used when dopamine or dobutamine fails to change the hemodynamic effects of severe CS or when dysrhythmias develop. Glucagon may be particularly useful when depressed LV function is related to the previous use of beta-blockers. Glucagon could induce well-marked hyperglycemia as a side effect.

A list of commonly used inotropic drugs with their doses and site of action is given in Table 2 (Box 5).

Combination of Inotropic Drugs and Vasodilator Therapy

Vasodilator therapy comprising of IV nitroglycerin can be combined with dopamine or dobutamine in a dose sufficient to allow of the benefits of vasodilatation and yet maintain an adequate systolic perfusion pressure of 90–100 mm Hg. Close monitoring of the PAEDP, arterial blood pressure, CO, tissue perfusion and the infusion rates of drugs is mandatory.

Table 2: Commonly used inotropic drugs with their doses and site of action

	Dopamine	*Dobutamine*	*Norepinephrine*	*Vasopressin*
Clinical indication	Cardiogenic shock, Vasodilatory shock, HF, Symptomatic bradycardia unresponsive to atropine or pacing	Low CO (decompensated HF, cardiogenic shock, sepsis induced myocardial dysfunction) Symptomatic bradycardia unresponsive to atropine or pacing	Shock (vasodilatory, cardiogenic)	Shock (vasodilatory, cardiogenic) Cardiac arrest
Dose range	2.0 to 20 µg/kg/min (max 50 µg)	2.0 to 20 µg/kg/min (max 40 µg)	8–30 µg/min	Infusion: 0.01 to 0.1 U/min (common fixed dose 0.04 U/min) Bolus: 40-U IV
Receptor Binding				
α_1	+ + +	+	+ + + + +	N/A
β_1	+ + + +	+ + + + +	+ + +	N/A
β_2	+ +	+ + +	+ +	N/A
DA	+ + + + +	N/A	N/A	N/A
V_1	N/A	N/A	N/A	+
V_2	N/A	N/A	N/A	+
Major side effects	Severe hypertension (especially in patients taking nonselective β-blockers), ventricular arrhythmias, cardiac ischemia, tissue ischemia/gangrene (high doses or due to tissue extravasation	Tachycardia, increased ventricular response rate in patients with atrial fibrillation, ventricular arrhythmias cardiac ischemia, hypertension (especially nonselective β- blocked patients) hypotension	Arrhythmias, bradycardia, peripheral (digital) ischemia, hypertension (especially nonselective β- blocked patients)	Arrhythmias, hypertension, decreased CO (at doses > 0.4 U/min), cardiac ischemia. Severe peripheral vasoconstriction causing ischemia (especially skin) Splanchnic vasoconstriction

V_1, receptors (vascular smooth muscle); V_2, receptors (renal collecting duct system); DA, Dopamine receptors
Abbreviations: CO, cardiac output; HF, heart failure.

Box 5: Management of fulminant pulmonary edema in cardiogenic shock

- Morphine 2–5 mg IV
- Reduce preload with IV nitroglycerin
- Increase cardiac contractility with inotropic support (dopamine, dobutamine)
- IV furosemide 100–250 mg, repeated if necessary or titrated IV infusion
- Combat hypotension with a titrated dose of noradrenaline (if necessary)
- Intubate and put on ventilator support with a high FiO_2

Abbreviation: IV, intravenous.

Use of Diuretics

Pulmonary edema warrants the use of an appropriate dose of furosemide either given as a bolus dose or a titrated IV infusion at the rate of 10–40 mg/hour. It is important to realize that following diuresis, the filling pressures of the left ventricle may fall to a point where the CO is further lowered, with a further drop in tissue perfusion. The filling pressure of the left ventricle should not be allowed to fall below 15–18 mm Hg.

Intra-aortic Balloon Counterpulsation (IABP)[1]

Severe CS characterized by marked hypotension, a very low CO and poor tissue perfusion is unlikely to respond to pharmacological measures described. Mechanical support with IABP should always complement and supplement these pharmacological measures.

Intra-aortic balloon counterpulsation should be instituted as quickly as possible *pari passu* with pharmacological measures, if possible even before transfer for diagnostic and therapeutic intervention to establish reperfusion. In the large National Registry of Myocardial Infraction, IABP was independently associated with survival at centers with higher rates of IABP use, whether PCI, fibrinolytic therapy or no reperfusion had been used.[27] Major complications occurred in 2.8%;[28] risk factors for complications include female sex, small body size, peripheral vascular disease.

Maintaining Oxygenation

It is important to ensure proper oxygenation by administering oxygen at a flow rate of 6–8 L/minute. A PaO_2 of less than 60 mm Hg, or respiratory distress, respiratory rate greater than 35/minute are clear indications for intubation and ventilator support. In fact, severe shock itself is an indication for respiratory support. Mechanical ventilation rests respiratory

muscles and reduces the oxygen cost of breathing, thus enabling oxygen to be used by the vital organs of the body. It also ensures adequate oxygenation and helps combat severe pulmonary edema. The FiO_2 should be set to allow oxygen saturation over 95%. Positive end-expiratory pressure (PEEP) should, if possible, be gradually increased, provided there is no marked hypotension, watching its effect on the blood pressure.

Correction of Electrolytes and Acid-Base Balance

Metabolic acidosis (lactic acidosis) is frequently observed and is due to poor tissue perfusion. Acidosis improves when tissue perfusion improves. If the pH is less than 7.25, it may need correction with an appropriate dose of IV sodium bicarbonate. A PaO_2 greater than 70 mm Hg should be maintained through the use of ventilator support using a high FiO_2 and PEEP. Increasing metabolic acidosis leads to cellular injury and further impairs myocardial function. Hypokalemia predisposes to ventricular dysrhythmias including ventricular tachycardia and fibrillation.

Correction of Factors that Aggravate Shock

Hypotension in MI may be potentiated by severe unrelieved pain, or it could also be partly related to the overuse of IV morphine or pethidine, sedatives and tranquillizers. Excessive use of diuretics can cause hypovolemia and hypokalemia leading to hypotension and weakness. Both supraventricular and in particular ventricular arrhythmias with fast ventricular rates need to be recognized and treated with drugs or if the need arises, by electroversion. Arrhythmias can cause a serious deterioration in the hemodynamic profile of such individuals. Bradyarrhythmias due to inferior wall infarction when marked, cause a sharp fall in CO and need to be corrected by IV atropine or by pacing. Persistent mild hypoxia can aggravate the dangers of hypotension as it is associated with decreased oxygen transport to tissues. The oxygen saturation must be maintained well over 90%. The danger of nosocomial infection is always present in a shock state particularly in patients with pulmonary edema who are on ventilator support. Such infections can tilt the balance against a patient who could have otherwise recovered. Finally, the deleterious hemodynamic changes produced by dysfunction and death of the myocardial wall can worsen into an irreversible state following a complicating pulmonary embolism. This may be difficult to diagnose against the background of CS. Pulmonary embolism if sufficiently severe is characterized by a high CVP, a high PAEDP and a PCWP which is significantly lower than the PAEDP. These are some of the contributory factors which singly or in combination can worsen the severity of shock in MI.

A great deal of attention continues to be paid over the last many years at attempts at myocardial preservation, i.e. providing better blood supply to ischemic muscle surrounding an area of infarction and thereby preventing ischemic muscle from undergoing further damage or death. Improvement of blood supply to ischemic muscle should improve pump function and help in relieving the state of shock. This in principle is theoretically sound, but is difficult to translate into practice. There are a number of unknown factors in relation to anatomy, collateral circulation, local blood flow within the coronaries, and metabolic requirements of ischemic or damaged myocardium, that operate in a given individual with MI. The best known method of helping to increase coronary blood flow is by administering an IV nitroglycerin drip which can reduce the work-load of the heart and which directly dilates the coronary vessels. The presence of marked hypotension prevents its use as is often the case. Some units continue to use IV glucose-potassium-insulin infusions (500 mL of 20% dextrose, 20 units insulin, 40 mEq KCl) in the hope that this may improve myocardial function. Short of interventional procedures like angioplasty which opens a culprit lesion within a coronary artery and directly improves blood supply, other methods of myocardial preservation are of dubious value.

Box 6: Monitoring of patients with cardiogenic shock in absence of invasive monitoring facilities

- Measure CVP via central line
- Monitor ECG, BP, heart rate, rhythm, temperature, O_2 saturation, arterial pH and blood gases
- High PAEDP or PCWP evidenced by—
  - CXR showing pulmonary edema
  - Clinically crepitations over lung bases, left ventricular diastolic gallop (audible third heart sound)
- Estimate CO and tissue perfusion clinically by noting—
  - Blood pressure
  - Skin temperature
  - Degree of sweating
  - Volume of peripheral pulse
  - Hourly urine output
  - General sensorium, and absence or presence of lactic acidosis
- Blood lactate level

Abbreviations: CVP, central venous pressure; PAEDP, pulmonary artery end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; CXR, chest X-ray; CO, cardiac output.

Management of Cardiogenic Shock in the Absence of Invasive Monitoring Procedures

Many ICUs or coronary care units in the country lack the facilities to monitor intra-arterial pressure through an intra-arterial cannula, or the PAEDP via the S-G catheter. Facilities for CO measurements are scarce. Fortunately, both gadgetry and technical expertise have improved significantly over the last decade, particularly in the large metropolitan cities. Even so, they are still in short supply (Box 6).

Almost all units can measure the CVP through a central line connected to a water manometer. The JVP can also be gauged clinically from the upper limit of pulsations of the internal jugular vein (with the head and neck elevated to an angle of about 45° from the horizontal). It is good clinical practice to tally the clinical measurement of the JVP with the actual

measurement of the CVP through a central line connected to a pressure gauge or to a manometer. Unfortunately, the CVP does not predict the PAEDP, a normal CVP being invariably associated with a high PAEDP in cases of CS.

A high PAEDP or PCWP is indirectly confirmed thus—

- *Clinically*, by noting the presence or absence of crepitations over the bases.
  If present, the degree and extent of crackles are noted. A LV diastolic gallop is always related to a raised LV filling pressure. An audible third heart sound generally indicates a PAEDP greater than 18 mm Hg.
- *Radiologically*, by a chest X-ray which can diagnose both interstitial and alveolar pulmonary edema. The chest X-ray is vital because on occasions (in about 30% of cases), the radiograph shows clear pulmonary congestion and even pulmonary edema which is not evident on auscultation. Gross pulmonary edema generally signifies a PAEDP greater than 30 mm Hg; varying but gradually increasing degrees of pulmonary edema are observed as the PAEDP rises above 20 mm Hg.

The arterial blood pressure by the cuff method is quite unreliable in the presence of severe vasoconstriction. Pressures may be unobtainable by the cuff method, but on monitoring via an intra-arterial catheter may be shown to be greater than 90 mm Hg. Impalpable radials or even brachials do not therefore signify irreversible shock in these individuals, but if the femorals are impalpable, or are barely felt, it always points to severe hypotensive shock. The CO and tissue perfusion can be judged clinically as best as possible by noting the skin temperature, the degree of sweating, the urine output, volume of peripheral pulses, general sensorium, the presence or absence of lactic acidosis and the overall clinical picture.

In the absence of invasive monitoring facilities, the following approach is recommended for the management of CS—

- Administer oxygen through high flow mask; monitor heat rate, rhythm, ECG tracing, CVP, blood pressure, O_2 saturation, X-ray chest, skin temperature, urine output, serum lactate. Frequent examination of the cardiorespiratory system.
- If there is no clinical and radiological evidence of pulmonary edema, use a volume load to raise the blood pressure and improve tissue perfusion. Stop the volume load when signs of pulmonary congestion become apparent clinically and/or radiologically. Then start on inotropic support and if needs be vasopressor support. If pulmonary congestion progresses to edema, use in addition a titrated dose of furosemide and a titrated dose of IV nitroglycerin.
- If definite well-marked pulmonary edema is already present, use inotropes and vasopressors. A titrated dose of IV nitroglycerin and IV furosemide will help to reduce preload. Fulminant pulmonary edema warrants intubation and mechanical ventilator support. Lesser degree of pulmonary edema may warrant the use of non-invasive ventilator support.

With increasing experience, we have been able to predict the hemodynamic profile on clinical and radiological examination, and by the clinical response to therapeutic measures in 70% of cases. This is a fairly satisfactory correlation with the actual measurement of pressures and CO, and should encourage good patient care in units lacking the monitoring facilities outlined earlier.

Reperfusion through Revascularization

The survival benefit of Early Revascularization (ERV) in CS has been convincingly demonstrated in the randomized SHOCK (Should We Emergently Revascularize Occluded Coronary Arteries for Cardiogenic Shock) trial.[9,20] In this trial, 302 patients with acute myocardial infarct and CS due to predominant LV failure were randomly assigned to an initial medical stabilization (IMS, n = 150) group, which included thrombolysis (63% of patients), intra-aortic balloon counterpulsation (80%) and subsequent revascularization (25%) or to an early revascularization group (ERV) (n = 152) which mandated revascularization within 6 hours of randomization and included angioplasty (55%) and coronary artery bypass graft surgery (35%). Results showed an increased benefit in survival at 1 year in the ERV group. The survival was 46.7% in the ERV group compared to 33.6% in the IMS group. The benefit was however apparent only in patients under 75 years.

Timing of Percutaneous Coronary Intervention

As in MI without shock, earlier revascularization in CS gives better results. Presentation 0–6 hours after symptom onset was associated with a lower mortality among CS patients in which door to angiography time was less than 90 minutes in about three quarter of patients.[29] In the SHOCK trial[9] there was an increase in the long-term mortality as time to revascularization increased from 0–8 hours. *However, as mentioned earlier there is a survival benefit as long as 48 hours after MI and 18 hours after shock onset.*

Stenting and Glycoprotein IIb/IIIa Inhibitors[30]

Stenting and Glycoprotein IIb/IIIa inhibitors have been shown to be independently associated with improved outcome in patients undergoing PCI for CS.

Percutaneous Coronary Intervention or Coronary Artery Bypass Graft Surgery

In the SHOCK trial,[9] 35% of patients in the ERV group underwent CABG at a median of 6 hours after randomization. Survival and quality of life was similar to those who underwent PCI even though the CABG group had a higher triple prevalence of left main disease, triple vessel disease and diabetes compared to the PCI group.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines[25] suggest that CABG is

the preferred method of revascularization in left main disease, severe triple vessel disease or in the presence of ventricular septal rupture or severe mitral regurgitation. PCI of the infarct related vessel is recommended in single or double vessel disease or in moderate triple vessel disease or when CABG is not possible for more extensive disease.

In perfect ICU and hospital set-ups, where prompt revascularization is offered to patients with CS following myocardial infarct, the mortality in the modern era is about 25%, far lower than older figure of 80–90%. Among CS patients undergoing PCI, age, time from symptom onset to PCI, post PCI, thrombolysis in myocardial infarction (TIMI) flow grade are independent predictors of mortality. Though ERV is increasingly practiced in Europe and America, developing world figures range from just 27% to 54%.[4]

How do these results in the West apply to conditions in India and other developing countries?

- Early revascularization as described in the SHOCK study is for logistic, economic and other reasons possible in very few units.
- In the present scenario the best possible approach for CS in MI is—
  - To thrombolyze the patient provided he is admitted to the Emergency unit within the first 6– 8 hours.
  - Stabilize the circulation with an aortic-balloon counterpulsation device and by pharmacological measures and then opt for revascularization, either a PCI or a CABG depending on the findings at coronary angiography.

Ventricular Assist Device and Extracorporeal Life Support[1]

Left ventricular assist device (VAD) supports circulation by drawing oxygenated blood from the left side of the heart and returning blood to the systemic arteries with either a pulsatile or continuous flow. This device may allow for recovering of stunned and hibernating myocardium and halt or reverse neurohormonal derangements.

Extracorporeal life support and VAD have been used sequentially as a bridge to cardiac transplant. To what degree these life support systems (even in expert hands) influence outcome is yet uncertain.

Treatment of Cardiogenic Shock due to Mechanical Complications[1]

Mechanical complications of MI in the form of a ruptured ventricular septum, ruptured papillary muscle, ruptured free wall are responsible for 12% of patients who present with or develop CS. Ventricular septal rupture has the worst prognosis, with a mortality of 87%.[31] The risk of these complications is higher with thrombolysis than primary PCI. The above mentioned mechanical complications should be strongly suspected in patients with a small infarct and shock. Both echocardiography and hemodynamic measurements can confirm the diagnosis.

Open heart surgery is advised in patients with mechanical complications. The use of an intra-aortic balloon counterpulsation together with pharmacological measures should help stabilize the circulation at least to some extent. *The sooner these patients are taken up for open heart surgery the better*. Waiting invariably ultimately results in a deteriorating circulatory state with multiple organ failure and a hopeless prognosis. There is a subgroup of patients with ventricular septal defect (VSD) where surgery is avoided because mortality is near 100%; this includes patients more than 75 years of age and those with a poor right ventricular function. Right ventricular function is an even more important determinant of outcome in ventricular septal rupture than LV function.[32,33]

Cardiogenic Shock in Pathologies Caused by Obstruction to Left Ventricular Outflow

Perhaps the commonest of these is tight aortic stenosis where the patient presents with cardiomegaly, absent or a faint systolic murmur in the aortic area and severe failure. The diagnosis can be clinically missed but is evident on an echocardiography. Emergency bypass surgery though carrying a considerable risk may be life saving if successful.

Hypertrophic obstructive cardiomyopathy can present with CS. The recognition of LV outflow obstruction is critical as hypotension in these patients is worsened by the use of diuretics or inotropes since both these agents will worsen obstruction. Treatment of CS due to hypertrophic obstructive cardiomyopathy consists of volume expansion and β-blockers. Pure agonists may be used to increase afterload, thereby increasing LV cavity size and decreasing obstruction.

Outflow obstruction at times causing CS is also observed in a rare condition termed Takotsubo cardiomyopathy which is characterized by extensive akinesia of apical zones with hyperkinesia of the rest of the myocardium, particularly the base. Alpha agonists may be helpful for their vasopressor effect and in severe cases an aortic balloon support device may tide the patient over a crisis. Low dose inotropes with careful monitoring of their effects have also been used.

Long-Term Survival and Quality of Life after Surviving Cardiogenic Shock

Result of the SHOCK trial reveals that 3 year and 6 year survival rates in the ERV group were 41.4% and 32.8% with persistence of treatment benefit.[20]

The quality of life importantly was far better than clinicians would ordinarily suppose. In patients with CS treated with ERV, 80% of survivors were asymptomatic at 18 months and all were in the New York Heart Association Functional Class I and II.

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CHAPTER 16

Sepsis and Septic Shock

GENERAL CONSIDERATIONS

Septic shock is the result of overwhelming infection. It can evolve with frightening, suddenness and severity and is frequently lethal. Severe sepsis is the second most important cause of death in intensive care units all over the world. However, sepsis and septic shock occurring from community-acquired infections outnumber sepsis and septic shock due to nosocomial infections. The epidemiological data from our country is lacking, but a recent study showed that 6% of all deaths in the United States from 1999 to 2005 were sepsis related and the age-adjusted rate of sepsis-associated mortality was 50.37 deaths per 100,000.[1] Some idea of the burden of sepsis in low and middle income countries (incidence per 1,000 patients-days) is given below in Table 1.

The mortality in septic shock even in good centers ranges from 40% to 60% despite the advances in antimicrobial treatment, and despite the intensive care provided to these patients.

The incidence of sepsis and septic shock appears to be increasing all over the world. Inadequate immune responses to infection due to underlying comorbid states, such as malignancy, lymphomas, leukemias, HIV infection, chronic hepatic or renal failure, diabetes, predispose to sepsis and septic shock. Infections in the aged and in the malnourished are also frequently followed by severe sepsis, septic shock and death. Iatrogenic infections induced by procedures or their complications in critical care units can also cause septic shock.

Table 1: Burden of sepsis in low and middle income countries (Incidence per 1000 patients-days). The Brazilian sepsis epidemiological study

Syndrome	*Incidence*	*Mortality (%)*
Sepsis	61.4	34.7
Severe sepsis	35.6	47.3
Septic shock	30.3	52.2
Zambia–30% of patients in a rural hospital had signs of sepsis		

Source: Brazilian Sepsis Epidemiological Study (BASES study). Critical Care 2004.

Septic shock chiefly follows Gram-negative bacterial infections. There is however, an increasing incidence of Gram-positive infections producing septic shock. The use of broad-spectrum antibiotics over prolonged periods of time, and organ transplantation, have brought in their wake fungal and viral infections which can also produce severe sepsis and septic shock. Important causes of severe sepsis associated with multiple organ failure in the tropics, in our experience, include fulminant tetanus, severe infections produced by *P. falciparum*, hemorrhagic dengue fever, typhoid, fulminant amoebic infections and acute disseminated hematogenous tuberculosis. These have been discussed at length in other sections of the book.

The important factors predisposing to the development of septic shock are listed in Box 1.

DEFINITIONS[2]

Definitions are a matter of semantics but it is important that clarity is introduced into the terminology used to describe various clinical profiles associated with sepsis. This would certainly help evaluate the results of management protocols in septic states. It has been increasingly realized over the last several years that the clinical features observed in sepsis, together with complications of shock and multiple organ failure can occur in other widely different conditions, which are unrelated to infection. An American College of Chest

Box 1: Important predisposing factors and causes of septic shock

- Infections in the aged, or malnourished
- Inadequate immune responses to infection due to underlying background disease, e.g. hepatic or renal failure, diabetes mellitus, malignancy, antimitotic drugs, HIV infection, lymphoma
- Iatrogenic infections induced by procedures in critical care units
- Virulent Gram-negative and Gram-positive infections
- Opportunistic infections (including fungal, viral) after prolonged antibiotic therapy, or following organ transplants, or in other immunocompromised patients, such as those with HIV infection and lymphoma
- Fulminant tetanus
- Hemorrhagic dengue fever
- Severe *P. falciparum* infections
- Disseminated hematogenous tuberculosis
- Fulminant *B. typhosus*, salmonella and amebic infections

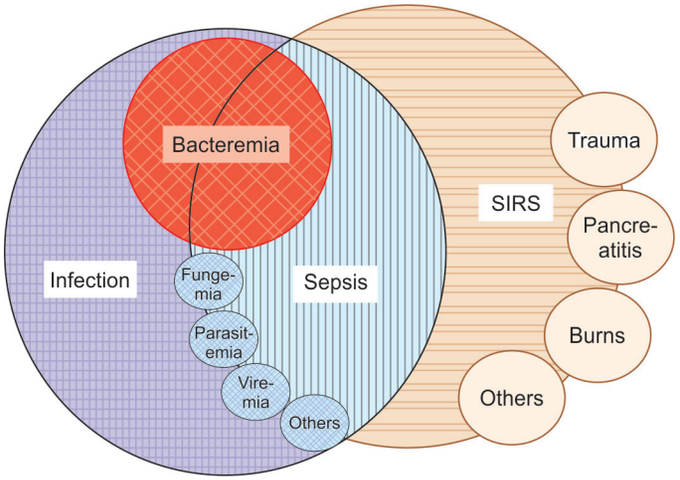


Fig. 1: The interrelationship between systemic inflammatory response syndrome (SIRS), sepsis and infection

Source: Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP-SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992:101:1644-55.

Physicians-Society of Critical Care Medicine (ACCP-SCCM) consensus conference held in 1991, proposed semantic terms that attempt to clearly define sepsis, and sepsis-related clinical states. This conference also proposed the use of the term systemic inflammatory response syndrome (SIRS) to include patients in whom the clinical features resembled sepsis, even though the etiology was due to noninfective causes. The proposed semantic definitions at this consensus conference are briefly described below.[3]

The SIRS is characterized by two or more of the following features: (1) body temperature greater than 38°C or less than 36°C; (2) heart rate greater than 90/minute; (3) hyperventilation greater than 20/minute or a $PaCO_2$ less than 32 mm Hg; or a white blood cell (WBC) count greater than 12,000/mm^3 or less than 4,000/mm^3 or greater than 10% band forms. A SIRS can occur following noninfectious causes, e.g. trauma, crush injuries, pancreatitis and burns. Also, SIRS even when primarily unrelated to infection can lead to hypotension, shock and to multiple organ failure. The consensus conference suggested that the term sepsis be used exclusively when a SIRS is due to infection. The interrelationship between SIRS, sepsis and infection is illustrated in Figure 1.

Severe sepsis is defined as sepsis associated with organ dysfunction, hypoperfusion or hypotension. Septic shock is defined as severe sepsis with hypotension that does not respond to adequate fluid replacement. It is associated with evidence of hypoperfusion and/or organ dysfunction.

These groupings, though arbitary, are useful and have been globally adopted both by clinicians and investigators. Their chief value lies in the evaluation and comparison of studies in patients with sepsis. The pathophysiological significance of these groupings remains to be established. Though the concept of the SIRS is excellent in that it can arise as an innate immune response to noninfectious causes and to infections, the criteria used to define SIRS are both nonspecific and mild in degree. Judging by the above mentioned criteria, most patients in a large teaching hospital in our country would not only have SIRS but would be dubbed as septic. Also the use of SIRS criteria to define septic shock is unrealistic. Shock from any noninfectious cause can also be associated with tachypnea, tachycardia and an increased WBC count. Again, the body temperature is often normal in septic shock. The SIRS criteria cannot therefore separate septic shock from other forms of shock. We have always maintained ever since the deliberations of the ACCP-SCCM consensus were published that the concept of SIRS should be retained but its criteria either changed or abandoned.

Several North American and European Intensive Care Societies agreed in 2001 to take a relook at the definitions of sepsis and sepsis related conditions.[4] This consensus conference came to the following conclusions—

- Current concepts of sepsis, severe sepsis and septic shock should remain unchanged.
- Current definitions do not allow for precise staging of the host response to infections.
- Signs and symptoms of sepsis are more varied than the initial criteria stated in 1991; the consensus included in the clinical features of sepsis, subtle changes involving one or more organ systems either detected clinically (Box 2), or on relevant laboratory tests.
- The future, according to this consensus conference, lies in developing a staging system that will characterize progression of sepsis. They suggest the PIRO concept of staging sepsis. This concept stratifies patients on the basis of their **P**redisposing conditions, the nature and extent of the **I**nsult (Infection), the nature and magnitude of the host **R**esponse, and the degree of concomitant **O**rgan dysfunction.

Box 2: Comparison between 1991 SIRS criteria to expanded list of signs and symptoms in 2001 Sepsis Definitions Conference

SIRS Criteria (1991)—

- Fever or hypothermia
- Tachycardia
- Tachypnea
- Altered white blood cell count

Sepsis Definitions Conference (2001)—

- General signs and symptoms include fever/hypothermia, tachypnea /respiratory alkalosis, positive fluid balance or edema—
  - General inflammatory reactions include altered white blood cell count, increased biomarker (C-reactive protein, IL-6, PCT) concentrations
  - Hemodynamic alterations include arterial hypotension, tachycardia, increased cardiac output or low systemic vascular resistance (SVR), altered skin perfusion, decreased urine output, hyperlactatemia (increased base deficit)
  - Signs of organ dysfunction include hypoxemia, coagulation abnormalities, altered mental status, hyperglycemia, thrombocytopenia, disseminated intravascular coagulopathy, altered liver function (hyperbilirubinemia), intolerance to feeding (altered gastrointestinal motility)

Abbreviations: SIRS, systemic inflammatory response syndrome; IL, interleukin; PCT, procalcitonin.

It has been proposed that the PIRO system could be used to stratify patients at or shortly after ICU admission. In fact the PIRO system has already been used to study ICU mortality in ventilator-associated pneumonia and in critically ill patients who had community acquired pneumonia.[5] Rubulotta and colleagues[6] used two large sepsis databases to validate a PIRO staging model risk stratification in severe sepsis. Clearly the system has the potential not only to stratify patients with sepsis with regard to prognosis, but would perhaps help to target specific therapy to specifically characterized subgroups. More studies are needed before this approach is widely accepted.

The consensus arrived at in 2001 noted the relative nonspecificity of the clinical features decided under SIRS. SIRS is often associated with increased levels of inflammatory markers in the blood—notably, the circulating concentrations of IL (interleukin)-6, procalcitonin (PCT), and C-reactive protein (CRP) are increased (Box 2). Perhaps, it may be possible in the future to use purely biochemical and/or immunological markers rather than clinical criteria to identify the inflammatory response. However, as yet, no large prospective studies lend support to such a hypothesis.

All the above-mentioned features listed in the Sepsis Definition Conference of 2001 (Box 2), could be subtle and mild, and need to be carefully searched for.

CLINICAL FEATURES

The clinical features of severe sepsis and septic shock include the following—

- Features of a SIRS due to an infection. These features include fever (or rarely hypothermia), tachycardia, tachypnea, and leucocytosis (or leucopenia <4000/mm^3).
- Systolic arterial blood pressure (BP) less than 90 mm Hg, or a mean arterial BP (MAP) less than 60 mm Hg. In hypertensive individuals, a fall of systolic arterial BP greater than 40 mm Hg below baseline is significant.
- Evidence of poor tissue perfusion as judged by a lactic metabolic acidosis or a sharp fall in urine output, and/or evidence of dysfunction of one or more organs or organ systems, either detected clinically or through laboratory tests.

The circulatory state is generally hyperdynamic, so that in addition to tachycardia, the pulse is bounding and of good volume, and the peripheries are warm.

There are certain important clinical pointers to impending severe sepsis and shock that need to be considered in a patient with infection or sepsis. These include the onset of unexplained tachypnea, the presence of a mild icterus, a subtle change in the mental state generally due to cerebral hypoperfusion and to metabolic changes, a fall in the urine output (< 50 mL/hour), mild metabolic acidosis, or the presence of a few purpuric spots. These all point to early organ dysfunction and may precede hypotension.

LABORATORY FEATURES

Besides showing leucocytosis or leucopenia, a coagulation profile may show evidence of an early disseminated intravascular coagulopathy (DIC). This includes an elevated prothrombin time, a decreased platelet count, decreased fibrinogen, increased fibrin degradation products, and increased thrombin index. Thrombocytopenia may often occur without evidence of DIC.

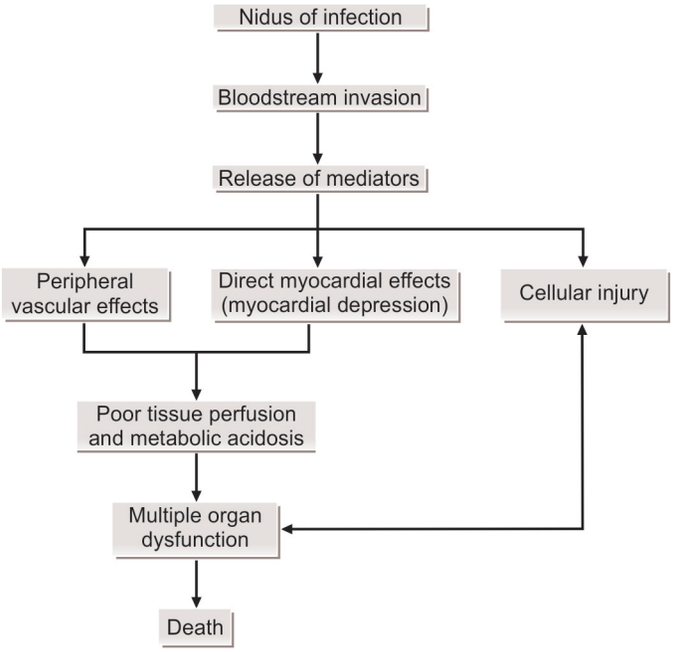
Hyperglycemia is common. Sudden marked elevations of serum glucose levels in patients on hyperalimentation may be the first indication of severe impending sepsis. Hypoglycemia is observed in the preterminal or terminal state of septic shock and signifies severe hepatic dysfunction. A rise in serum bilirubin, serum aminotransferases, and in the alkaline phosphatase, occurs very frequently and points to hepatic dysfunction.

The hypermetabolic state is evinced by a marked increase in the urinary urea or urinary nitrogen over 24 hours, and a negative nitrogen balance.

The arterial pH may be low in the presence of metabolic acidosis and early involvement of the lung is manifested by a mild to moderate hypoxia with hypocapnia.

Cytokines (especially IL-6 and IL-8), CRP , and PCT levels have been noted to rise significantly in sepsis. Literature review[7] indicates that there are many biomarkers that can be used in sepsis, but none have sufficient specificity or

Flowchart 1: Pathogenesis of severe sepsis and septic shock



sensitivity to be routinely employed in clinical practice. PCT and CRP have been most widely used, but even these have limited abilities to distinguish sepsis from other inflammatory conditions or to predict outcome. In view of the complexity of the sepsis response, it is unlikely that a single ideal biomarker will ever be found. A combination of several sepsis biomarkers may be more effective, but this requires further evaluation.[7]

PATHOPHYSIOLOGY[8-11]

A description of current research on this subject would fill a volume. This section merely gives a basic brief description of the pathophysiology of septic shock to enable a better comprehension of sepsis and its complications; difficulties in management would then be more easily appreciated (Flowchart 1).

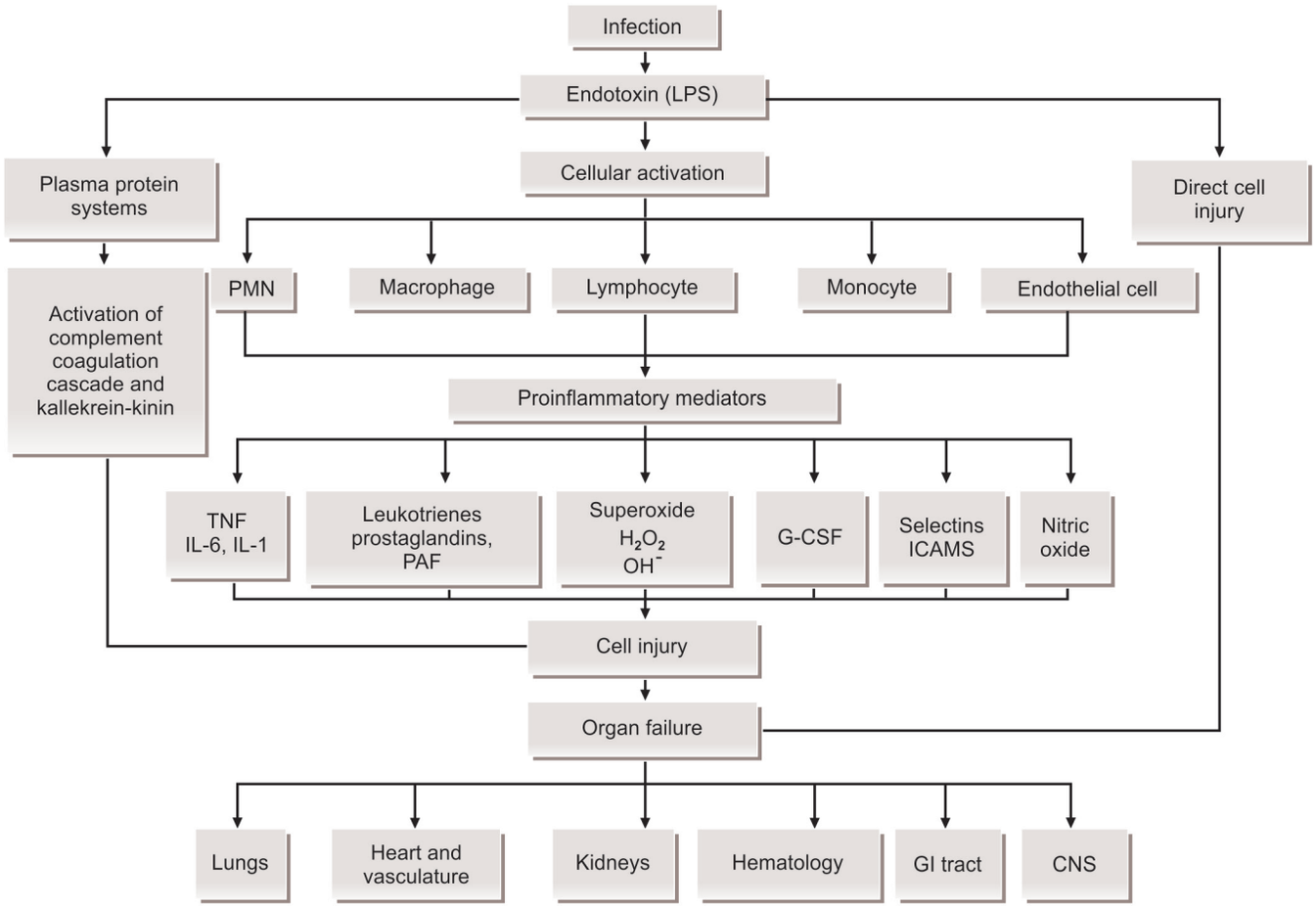
Classically septic shock is due to endotoxins released by Gram-negative bacteria. Recent investigations have implicated cell wall components of both Gram-negative and Gram-positive organisms. Septic shock can also occur with fungal infections, viral infections, as well as protozoal infections, notably *P. falciparum* infections, or for that matter can result from any pathogenic microorganism. Studies on septic shock have however been chiefly in relation to endotoxin produced by Gram-negative bacteria. Endotoxin is a lipopolysaccharide component of the outer membrane of the bacterial cell. It consists of oligosaccharide side chains, a core polysaccharide and lipid A, the latter being highly antigenic and believed to be responsible for the features of clinical sepsis. Endotoxin is directly toxic to endothelium and tissue cells, contributing to diffuse endothelial and tissue injury that characterizes the sepsis syndrome. Endotoxin interacts with normal host defenses and triggers the release of numerous mediators—IL-1, granulocyte monocyte-colony stimulating factor, tumor necrosis factor (TNF-α) and procoagulant activity factor. Endotoxin initiates the release of cytokines from mononuclear cells, in particular of TNF-α which is responsible for a number of features of the sepsis syndrome. Endotoxin also activates neutrophils with the subsequent release of proteases and oxidants which promote endothelial and tissue cell damage, degrade matrix and generate other proinflammatory mediators. A degradation of arachidonic acid is observed in cell walls through phospholipase. The mobilized arachidonic acid from the leucocyte cell can follow two pathways—the cyclo-oxygenase pathway leading to the formation of thromboxanes and prostaglandins, and the lipo-oxygenase pathway leading to the formation of leukotrienes. These mediators have various actions, some of them deleterious to tissue integrity and function. Phospholipase A2 also releases membrane bound phospholipids which are converted to the platelet activating factor (PAF). The latter is known to increase vascular permeability, increase production of toxic oxygen free radicals, and activate platelets and phagocytes.

Recent attention has been focused on the role of toxic oxygen metabolites, in particular nitrous oxide (NO). Activated phagocytes produce oxygen radicals that kill bacteria. A leakage of these products from the cell can cause tissue damage. Endothelial derived relaxing factor (EDRF) is another toxic free radical which chemically is NO. While small quantities of NO can improve blood flow in the microcirculation, larger quantities can produce vasodilatation and hypotension. NO can be produced from several cell lines including vascular endothelium and polymorphonuclear cells. NO synthetase is induced by endotoxin and TNF-α; it produces NO from L-arginine.

Endotoxin also activates factors within the serum. It thus activates and stimulates the coagulation pathway. This can occur at multiple sites. Research has focused increasing attention on the roles of endothelial injury and coagulation in sepsis.[8] Sepsis can be conceptualized as a loss of homeostasis, caused by an imbalance of opposing mechanisms that normally maintain this homeostasis. On one side are coagulation and inflammation, actively promoted by endothelial injury, thrombin production, tissue factor expression and proinflammatory mediators. On the opposite side is fibrinolysis. Fibrinolysis normally counters the procoagulant factors, but is suppressed in sepsis. The suppression of fibrinolysis is perhaps related to several factors, notably increased levels of plasminogen activator inhibitor-1 (PAI–1), thrombin-activable fibrinolysis inhibitor (TAF-Ia) and decreased levels of Protein C. The homeostatic imbalance prevailing in sepsis is believed to lead to microvascular thrombi in various organ systems. This could be the driving force that culminates in increasing multiple organ dysfunction and death.

In summary, invasive infection of the body by microorganisms and their products or toxins elicits a strong response

Flowchart 2: The role of mediators in severe sepsis and septic shock



from the host defenses.[11] The response is characterized by activation of cellular elements and of the plasma protein systems. The cells activated include the mononuclear cells, lymphocytes, macrophages, neutrophils and endothelial cells. The activated cells produce numerous cytokines and mediators, some of which are proinflammatory and some anti-inflammatory. The host defense mechanisms also activate complement, the coagulation cascades and the kallikrein-kinin systems. Current thinking conceptualizes sepsis as a loss of homeostasis in which procoagulant forces predominate over fibrinolysis.

If the host defense response is disorganized, unorchestrated, unbalanced and unchecked it fails to defend the host and paradoxically enough inflicts injury on the host. This injury is widespread because of the toxic effect of numerous mediators, and also because of endothelial damage and the dominance of procoagulant factors leading to microvascular thrombi in various organ systems. The clinical features of severe sepsis, septic shock, and the evolution of multiple organ dysfunction and failure are a consequence of the changes described above. Flowchart 2 illustrates the role of mediators in severe sepsis and septic shock. Figure 2 illustrates the loss of homeostasis in severe sepsis.

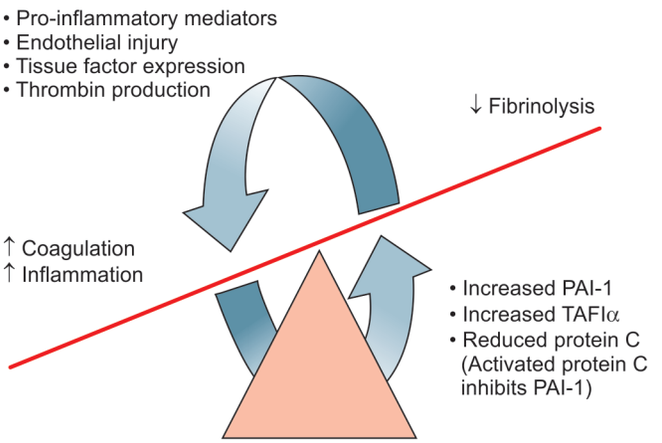


Fig. 2: Loss of homeostasis in severe sepsis

Source: From Lilly Data on File, Elli Lilly and Company (India) Pvt. Ltd.

HEMODYNAMIC EFFECTS

The hemodynamic effects of severe sepsis typically result in a high output hyperdynamic circulatory state with tachycardia and hypotension. Septic shock in addition to the

above is characterized by systolic BP less than or equal to 90 mm Hg not responding to fluid replenishment. It is associated with evidence of hypoperfusion and/or organ dysfunction. The hemodynamic state outlined holds not only for bacterial infections, but severe infections caused by other microorganisms, including fungal and viral infections, as also fulminant infections peculiar to the tropical and developing countries of the world.

The high cardiac output and the hyperdynamic circulatory state in severe sepsis and septic shock could well be a compensatory response to increased tissue metabolism.[12] This is certainly true for the hemodynamic profile of severe tetanus where a hyperdynamic circulatory state is observed even in paralyzed patients on ventilator support.[13,14]

The hemodynamic effects of severe sepsis and septic shock can be considered under the following heads—

Peripheral Vascular System

- There is a marked decrease in the arterial and venous tone resulting in venous and arteriolar dilatation with a fall in peripheral vascular resistance, and therefore a fall in the systemic arterial BP. The smaller arterioles are chiefly affected whereas venous tone is most reduced in the larger capacitance vessels. These changes are greatest in the areas of active infection and inflammation. Hypotension in septic shock is associated with complement activation and with increased TNF-α, IL-1 levels. Other vasodilating substances include nitric oxide, endothelial relaxing factor and PAF. Bernard et al.[15] have provided further insight into the mechanism of sepsis induced vasodilatation and hyporesponsiveness to vasoconstrictor drugs. Their study implicates macrophage derived mediators that affect smooth muscle contractility via nitric oxide synthesis. Catecholamine alpha-receptor downregulation has been experimentally reported, and if applicable to humans, may account for the poor vasoconstrictor response to vasopressors.

  The microvascular circulation has been shown to be adversely affected, contributing thereby to tissue hypoxemia and the frequent evolution of multiple organ failure. De Becker and colleagues[16] noted that the density of the microvasculature was markedly reduced in severe sepsis, with a sharp reduction in the proportion of perfused small vessels. A new technique, termed orthogonal polarization spectral imaging was used to measure sublingual microcirculation, as representative of the vascular bed. This new technique may help to elucidate the mechanisms involved in reduced microvascular blood flow in severe sepsis and septic shock.
- A generalized increase in vascular permeability is also noticed in septic shock with increase in interstitial fluid and tissue edema. A peripheral pooling, hepatosplanchnic pooling, and at times fluid loss from the gastrointestinal tract is responsible for a fall in effective circulatory volume.
- The combined effect of the above two factors leads to hypovolemia which may not be overt; this can at times mask the underlying hyperdynamic state, which becomes evident on fluid repletion.
- There is a change in the pattern of blood flow distribution in septic shock. Some organs receive a supranormal supply of oxygen, whereas others are rendered ischemic. This is of particular importance in the splanchnic circulation. Hepatovenous desaturation has been reported in septic patients.[17]
- Changes in oxygen delivery, oxygen uptake and oxygen use or consumption by tissues are dealt with later.

Heart[18]

Myocardial depression is present in almost all patients with septic shock. Decreased compliance with decreased left ventricular diastolic function is observed. Left ventricular systolic function is also reduced as evinced by a dilated cardiomyopathy with a low ejection fraction and a reduced ventricular stroke work index. Cardiac output is usually increased because of marked tachycardia. Myocardial depressant factors include TNF-α, low molecular weight soluble molecules and lipid soluble substances. There is no evidence of myocardial ischemia, the coronary blood flow being well maintained. There is evidence of beta-receptor downgrading and this may be responsible for the poor response to inotropic drugs which is often observed in these patients. In the absence of severe hypovolemia, the net result is a hyperdynamic circulation with increased cardiac output due to increased heart rate.

Pulmonary Hypertension

Pulmonary hypertension due to increased pulmonary vascular resistance is frequently present particularly when septic shock produces the acute respiratory distress syndrome (ARDS). When significant pulmonary hypertension develops, right ventricular function may be markedly affected due to an increased afterload.

Tissue Oxygenation

Tissue oxygenation eventually always suffers in septic shock. There is an increase in lactic acid production with metabolic acidosis.

Hemodynamic Profiles in Septic Shock[19]

The hemodynamic profile is dependent on the stage of shock—early or late, on the compensatory mechanisms present, on the presence and degree of myocardial dysfunction in the septic state, on the presence and degree of associated hypovolemia, and the therapy the patient may have received prior to admission to the ICU.

- The most characteristic pattern in the early stage is a hyperdynamic circulation characterized by a high cardiac index (CI at times as high as 7 L/m^2) with tachycardia, a low systemic vascular resistance (SVR), a low pulmonary capillary wedge pressure (PCWP) and hypotension. The early stage of severe sepsis and septic shock is characterized by peripheral vasodilatation so that the pulse is

bounding and the peripheries warm. The high CI is due to tachycardia and not to increased contractility. In fact, as has been discussed already under Hemodynamic Effects, both systolic and diastolic functions of the heart are depressed in spite of the high cardiac output. The left ventricular ejection fraction (LVEF) typically falls to as low as 20–30% in the first 24–48 hours. During this period the left ventricle dilates and abnormalities in both systolic and diastolic function are observed. The left ventricle responds abnormally to a volume load, in that the reduced left ventricular stroke work increases marginally or to a very small extent. In survivors, a reversal of this abnormal function is observed over 7–10 days.

- In the late stage of severe sepsis and septic shock, particularly in patients who are likely to succumb, the cardiac function remains poor or continues to deteriorate. The profile likely to be observed is a normal or a slightly low CI, an increasing PCWP, a normal SVR or a SVR showing a trend towards a slow increase. Persistent or increasing hypotension poorly responsive or unresponsive to therapy is observed.
- The preterminal stage of septic shock is often associated with a low CI, a high PCWP and an increased systemic vascular resistance. Marked tachycardia, with hypotension unresponsive to all therapy is observed.

Though the last profile is preterminal or in the late stages of septic shock, some patients with fulminant septic shock may have a very low CI with a high SVR soon after its onset. At times, hypovolemia may strongly contribute to this profile and this is recognized by low filling pressures. However, in a few individuals the PCWP is high, so that the hemodynamic profile is similar to that seen in severe cardiogenic shock.

The various hemodynamic profiles in septic shock are shown in Box 3.

Frequently observed left heart pressures and cardiac output in septic shock vis-à-vis the values in cardiogenic, cardiac compressive, hypovolemic shock and anaphylactic shock are detailed in Table 2.

Box 3: Various hemodynamic profiles in septic shock

Early stage—tachycardia, hypotension, low PCWP, high CI, and low SVR

With progression of the syndrome and deteriorating cardiac function—hypotension, increasing PCWP, normal or slightly low CI, normal to rising SVR

Late (preterminal) stage—hypotension, high PCWP, low and progressively decreasing CI, and increased SVR

Rarely, very low CI, high PCWP and high SVR is seen at the start in fulminant septic shock (profile resembles cardiogenic shock)

Abbreviations: CI, cardiac index; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

Table 2: Frequently observed left heart pressures and CO in septic shock, cardiogenic shock, cardiac compressive shock, hypovolemic shock and anaphylactic shock

Types of Shock	*PCWP (mm Hg)*	*CO (mL/min)*
Septic shock	↓ or Normal	↑↑ or Normal
Cardiogenic shock (following acute MI)	↑↑	↓↓
Cardiac compressive shock (Cardiac tamponade)	↑↑	↓ or ↓↓
Hypovolemic shock	↓↓	↓↓
Anaphylactic shock	↓ or Normal	↑ or Normal

Abbreviations: CO, cardiac output; PCWP, pulmonary capillary wedge pressure.

Oxygen Delivery (DO_2) and Oxygen Uptake ($\dot{V}O_2$) in Severe Sepsis and Septic Shock[20]

In the early and evolving phase of severe sepsis and septic shock, there is an increase both in DO_2 and in $\dot{V}O_2$. Even though there is an increase in oxygen consumption it may not be enough for the increased tissue need for oxygen, so that tissue hypoxia can still occur. Oxygen extraction ratios may be increased at this stage. Shoemaker[21] in a large prospective study of patients in septic shock, reported that survivors had a higher CI, a higher DO_2 and a higher $\dot{V}O_2$ than nonsurvivors. In the late phase of septic shock, oxygen consumption may fall sharply even though DO_2 is satisfactory, resulting in a low oxygen extraction ratio. Decreased oxygen extraction and consumption could well be related to the presence of the microcirculatory mitochondrial dysfunction syndrome (MMDS). MMDS as the name suggests is due to an impaired microcirculation which prevents adequate oxygen from reaching tissue cells and/or disturbed mitochondrial function within tissue cells, so that oxygen cannot be utilized by the cells. The MMDS is discussed later in this chapter.

Relation between Oxygen Uptake ($\dot{V}O_2$) and Oxygen Delivery (DO_2) in Septic Shock

In normal individuals (normal physiology), the oxygen consumption ($\dot{V}O_2$) is dependant on tissue demands and is independent of oxygen delivery. Once oxygen delivery falls below a critical level, DO_2 critical, the $\dot{V}O_2$ becomes linearly dependant on DO_2. Anaerobic metabolism then sets in resulting in lactic acidosis. In severe sepsis, septic shock, the $\dot{V}O_2$-DO_2 relationship shifts upwards and to the right. This is due to alterations in distribution of blood flow which impairs the ability of the tissues to extract oxygen from the perfusing blood. The dependency of $\dot{V}O_2$ on supply (DO_2) is thus observed over a wider range of oxygen delivery values than usual, in patients with septic shock. See Figures 3 and 4.

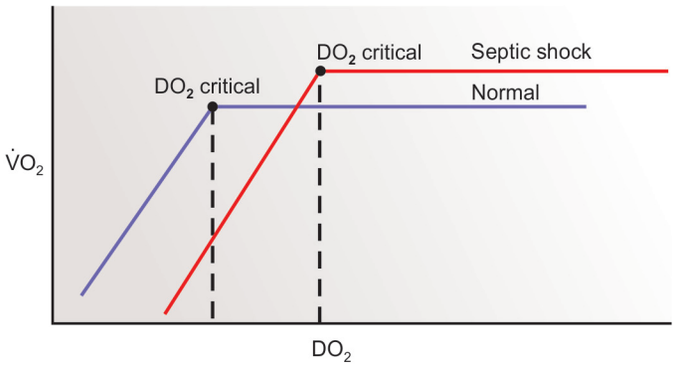


Fig. 3: In severe sepsis and septic shock, the relation between DO_2 and $\dot{V}O_2$ shifts to the right and upwards of the normal physiological DO_2-$\dot{V}O_2$ relation

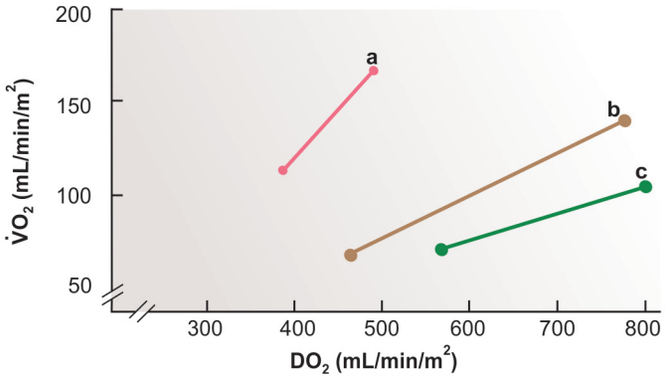


Fig. 4: Oxygen consumption ($\dot{V}O_2$) plotted against oxygen availability (DO_2) in normals (a), and in patients with septic shock (b and c). Note that as the severity of septic shock increases (b and c), the slope of the $\dot{V}O_2$-Oxygen availability relationship decreases, pointing to an inability of the tissues to utilize oxygen in spite of adequate oxygen availability

MANAGEMENT[22,23]

Severe sepsis has been divided into two stages: (1) early and (2) late with reference to its management. The first 0–6 hours is the early stage of sepsis—the golden hours during which a quick diagnosis is made and goal directed therapy instituted according to the seminal work of Rivers and colleagues[22] and the subsequent international guidelines laid down in the Surviving Sepsis Campaign (SCC).[23] In sepsis, the transition to an increasingly serious illness occurs during these 'golden' six hours when quick diagnosis and prompt management can lead to better outcome. The onset and progression of severe sepsis and septic shock is characterized by an imbalance between oxygen delivery and oxygen demand resulting in global tissue hypoxia and ultimately in multiorgan dysfunction and failure. The purpose of early goal directed therapy (EGDT) is to try and rectify this imbalance thereby reducing morbidity and mortality.

The priority tasks which should be performed within 6 hours of severe sepsis and septic shock are—

- Hemodynamic stabilization or resuscitation.
- Restoring tissue oxygenation.
- Use of lung protective ventilation if ventilatory support is deemed necessary.[24]
- Infection identification and infection control (antibiotic therapy and source control).[25]

It is crucial to commence resuscitative measures to restore hemodynamic stability promptly as soon as the diagnosis is made—at home if this is feasible before awaiting transfer to the hospital, in the ambulance, in the emergency department (ED), in the ward or on admission to the ICU. In India, though treatment is often first initiated in the ED, patients are quickly shifted to the ICU where better trained personnel, better monitoring and better facilities are available.

Initial Assessment

The first priority in a patient with severe sepsis or septic shock is to stabilize the airway, administer oxygen through a high flow mask and if there is significant respiratory distress or hypoxia to initiate ventilatory support. Of equal importance comes an assessment of perfusion—the heart rate and rhythm, the blood pressure, skin temperature, capillary refill, mental state and the urine output over the last 4–6 hours, if this information is available. On admission to the ED or the ICU, the heart rate, respiratory rate, temperature, electrocardiogram (ECG) and oxygen saturation are continuously monitored. As soon as this initial assessment is made, restoration of tissue perfusion through improvement of the circulatory state is promptly begun. Other measures, in particular identification of the nature of infection and measures to control infection (antibiotic therapy and source control) should be taken *pari passu* or soon after efforts to restore hemodynamics of the circulation have begun.

Hemodynamic Stabilization and Improvement of Tissue Oxygenation

The goals of initial resuscitation[22,23] in severe sepsis, septic shock are—

- Central venous pressure (CVP) of 8–12 mm Hg. If a patient is mechanically ventilated, a higher central venous target 12–15 mm Hg is recommended.[26]
- Mean arterial blood pressure 65 mm Hg or greater.
- Urine output 0.5 mL/kg per hours or preferably more.
- Central venous or mixed venous oxygen saturation greater than or equal to 70% or greater than or equal to 65%, respectively.
- No base deficit, a normal pH and normal or reduced lactate level in the blood.

Achievement of the above goals during hemodynamic resuscitation necessitates the insertion of a central venous catheter to measure CVP. Though the initial BP is measured by a sphygmomanometer, an arterial line is preferable particularly in patients who are hypotensive as in many hypotensive patients, the BP readings recorded by a sphygmomanometer are much lower than what they actually are. Hourly urine output through a Foley's catheter is essential.

The central venous oxygen saturation measured via the central venous catheter is currently felt to be a fairly good substitute for the mixed venous oxygen saturation as measured through the pulmonary artery catheter.

Volume Resuscitation

The initial measure towards achieving the goals stated above is volume resuscitation. Volume resuscitation should commence promptly through a 14F gauge catheter inserted into a peripheral vein. It should not await the insertion of a central venous catheter (see Chapter Hypovolemic and Hemorrhagic Shock) for fluid infusion, or the insertion of an arterial line for accurate measurement of BP. In the ED, or in the ICU the central venous line and an arterial line can be inserted by one intensivist, while another intensivist starts volume resuscitation.

Initial volume resuscitation should be performed with either 1,000 mL of a crystalloid solution (0.9% normal saline or a Ringer lactate solution) or 300 of a colloid (5% albumin) over 30 minutes. The saline versus albumin fluid evaluation (SAFE) study[27] concluded that in patients in the ICU use of 5 % albumin or normal saline for fluid resuscitation resulted in similar outcomes at 28 days. Even so, for quick resuscitation in severely hypotensive patients both colloids and crystalloid can be infused together, or the initial infusion of a colloid solution is followed by an ongoing infusion of crystalloids (see Chapter Hypovolemic and Hemorrhagic Shock). Volume status, tissue perfusion and BP are monitored on an ongoing basis. Further infusion of fluids is continued till hemodynamic improvement continues and the goals of hemodynamic resuscitation are met. The central venous pressure should not be pushed beyond 12 mm Hg or beyond 15 mm Hg if the patient is on mechanical ventilation support. Patients in severe septic shock have large volume deficits and many require as much as 8–10 L of crystalloids or 2–4 L of colloids in the first 24 hours.[22]

Use of Vasoactive Drugs and Inotropes

If after volume infusions have raised the CVP to 12 mm Hg, the MAP is less than 65 mm Hg, vasopressors and/or inotropes are indicated. Norepinephrine is generally recommended as the first line drug starting with 2–4 μg/minute and progressively increasing the dose so as to obtain a MAP greater than 65 mm Hg.[22] It is wise not to exceed a dose greater than 30 μg/minute as larger doses are not only infructuous but may well do harm. According to the SSC guidelines,[23] epinephrine (added to and potentially substituted for norepinephrine) can be used as an additional agent to maintain adequate BP. Vasopressin in a dose of 0.03 units/minute (according to the SSC guidelines) can be added to norepinephrine with intent of either raising MAP or decreasing norepinephrine dosage. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension. Vasopressin in doses higher than 0.03–0.04 units/minute should be reserved for salvage therapy. According to the guidelines, dopamine is best used only in highly selected patients (e.g. patients with low-risk of tachyarrhythmias and absolute or relative bradycardia). Even so, in many critical care units, dopamine remains the drug of choice after norepinephrine in patients with septic shock. When administered in a dose greater than 10 μg/kg per minute, dopamine has both a strong vasopressor effect plus an inotropic action. The latter is particularly useful in patients with septic shock who have myocardial dysfunction. Dopamine is often combined with dobutamine in these patients. The dose of dopamine should not exceed a maximum of 30 μg/kg per minute—further increase is not likely to help and in all probability does more harm and may have to be omitted in patients with marked tachycardia or arrhythmias. Low-dose dopamine is no longer recommended for renal protection.[23]

Rivers and associates[22] mention in their protocol for Early Goal Directed Therapy that if the MAP is greater than 90 mm Hg, vasodilators are given until it is brought down to 90 mm Hg or below.

Vasopressors can unquestionably increase the arterial BP but their powerful vasoconstrictor properties could produce increasing organ ischemia and adversely affect cardiac output by markedly increasing the afterload. In patients with septic shock who have sepsis induced myocardial dysfunction this could do more harm than good to the circulatory state and to tissue perfusion.

Vasopressors and inotropes should always be given through a central line. Sinus tachycardia and tachyarrhythmias are important complications of these drugs and may prevent the use of an appropriate dose. A rare but feared complication particularly with dopamine administration is ischemic limb necrosis. Phentolamine in an intravenous (IV) bolus dose 5 mg followed by an infusion of 1 mg/minute should be given at the earliest sign of limb ischemia. Phenylephrine though recommended in selected situations is barely used in most critical care units except perhaps as salvage therapy.

Use of Dobutamine

If after a volume load has pushed the CVP to the required level and if in spite of the use of vasopressor support the central venous oxygen saturation ($ScvO_2$) is less than 65%, dobutamine is administered as an IV infusion starting with 5 μg/kg per minute, going up to 20 μg/kg per minute. Dobutamine is particularly useful in the presence of sepsis induced myocardial dysfunction.

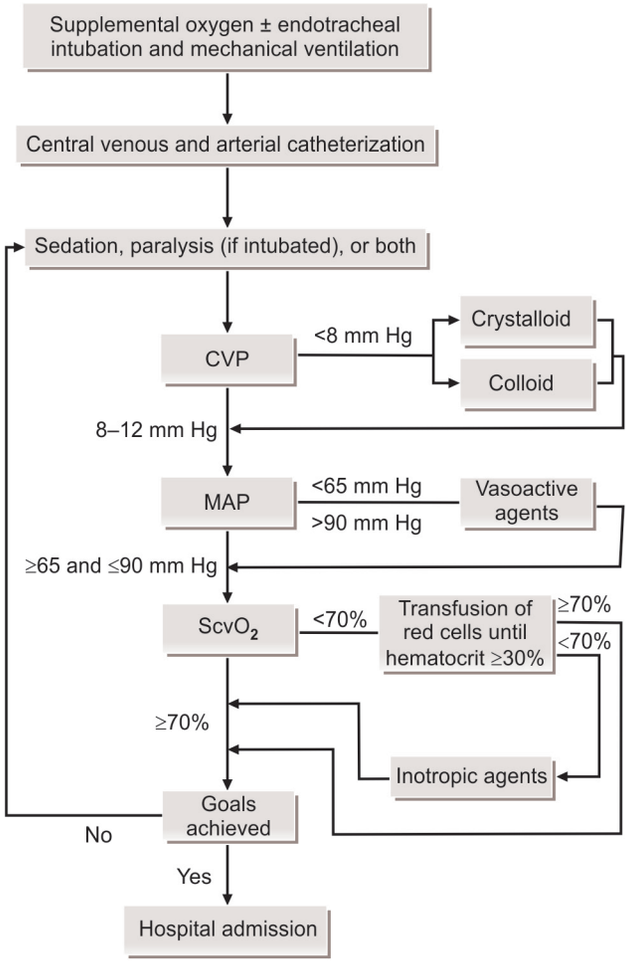
Packed Red Blood Cell (RBC) Infusion

Rivers and colleagues[22] in their work on EGDT recommend that the packed cell volume (PCV) if low is raised to 30% by infusion of packed RBCs in order to improve the oxygen carrying capacity of blood and thereby help in the relief of tissue hypoxia. The steps in EGDT are illustrated in Flowchart 3.

Laboratory and Other Investigations in 0–6 hours

A laboratory evaluation should include a complete blood count with white blood cell differentiation, blood culture,

Flowchart 3: Components of EGDT as per Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368-77.



Abbreviations: EGDT, early goal-directed therapy; CVP, central venous pressure; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation.

PCT, erythrocyte sedimentation rate (ESR), CRP, blood chemistry, arterial pH and blood gas values and arterial blood lactate. Laboratory tests to evaluate organ function should be done on admission. These include an assessment of renal function—electrolytes, blood urea nitrogen (BUN) and creatinine and an assessment of hepatic function which includes serum bilirubin, aspartate aminotransferase (AST), alkaline phosphatase and serum proteins. The coagulation profile including prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT) and platelets should be tested. Blood for the above tests and blood cultures should be sent to the lab as soon as a peripheral vein has been secured. Urine culture, culture from wounds, discharges and other body fluids if relevant should also be asked for. An appropriate antibiotic or a combination of antibiotics is administered intravenously in an appropriate dose as soon as those cultures have been sent. Evaluation of the above laboratory investigations should be on an on-going basis, being repeated at appropriate intervals.

Table 3: Techniques for measuring blood flow and tissue oxygenation

Technique	*Arterial or venous access required?*	*Suitable for all patients?*
External Doppler	No	Yes
Esophageal Doppler	No	No, the patient must be sedated
Thoracic bioimpedance	No	No, the patient must have normal anatomy and access to the neck
Exhaled CO_2 Fick method	No	No, the patient must be on a ventilator
Pulse contour	Yes	No, the patient must have at least an arterial line in place
Pulmonary artery catheter	Yes	No, the patient must have a central line in place

Source: Modified from Ahrens T. Hemodynamics in sepsis. AACN Adv Crit Care. 2006;17(4):435-45.

Other investigations include—

- An X-ray chest (portable in the ICU or ED).
- USG of the abdomen and pelvis.
- Further imaging [e.g. computed tomography (CT), magnetic resonance imaging (MRI)] should be organized after the patient is stabilized and that too if appropriate and necessary.
- Tests to identify the source of sepsis—
  - Blood cultures have already been mentioned.
  - Sputum examination—smear, culture and sensitivity.
  - Urine routine, culture and sensitivity.
  - Examination of other fluids or discharge from wounds, secretions.
  - Examination of cerebrospinal fluid (CSF), if necessary.

Monitoring Hemodynamic Perfusion and Tissue Oxygenation during Resuscitation

Monitoring CVP and MAP is easy. However, even when resuscitation goals for CVP and MAP are achieved, poor tissue perfusion and tissue hypoxia may persist. This is indicated by raised lactate levels and lowered $ScvO_2$ levels, both of which require to be monitored. An increased lactate level and a lowered $ScvO_2$ point to the need for renewed resuscitative efforts. The ultimate goal of resuscitation in septic shock is the abolition of tissue hypoxia through an adequate oxygen supply to meet tissue requirement. Ideally, measurements of tissue perfusion and oxygenation are necessary to determine if this has been achieved.

Blood flow measurements are not frequently done because of the difficulties associated with the use of available invasive techniques.[28] Newer less invasive techniques such as external and esophageal Doppler, thoracic impedance are being increasingly employed by clinicians in the West (Table 3).[28,29] Except for the external Doppler, these noninvasive techniques

Table 4: Techniques for measuring tissue oxygenation

Measure	*Method*	*Variables*	*Global or regional*	*Invasive or noninvasive*
Established techniques—				
Systemic oxygenation	PAC	$\dot{V}O_2/DO_2/ERO_2$	Global	Invasive
Mixed venous O_2 saturation	PAC–blood gas analyses	$S\dot{v}O_2$	Global	Invasive
Central venous O_2 saturation	CVC (right atrium)–fiber optic cable	$ScvO_2$	Global	Invasive
Lactate	Laboratory–enzymatic testing	Lactate	Global	Invasive
Emerging techniques—				
Gastrointestinal tonometry and sublingual capnography	Measurement of pCO_2 in an air-filled or saline-filled balloon; use of sublingual probe	$prCO_2/pCO_2$ gap, pHi, sublingual pCO_2	Regional	Minimally invasive
Near-infrared spectroscopy	Near-infrared absorbance analysis	Hb/O_2Hb, cytochrome aa_3	Regional	Noninvasive
Tissue oxygen tension	Polarographic probes	pO_2	Regional	Minimally invasive

Abbreviations: PAC, pulmonary artery catheter; CVC, central venous catheter; $\dot{V}O_2$; oxygen consumption; DO_2, oxygen delivery; ERO_2, systemic O_2 extraction ratio, Hb, hemoglobin; $S\dot{v}O_2$, mixed venous oxygen saturation; $ScvO_2$, central venous oxygen saturation; pHi, gastric intramucosal pH.

are not suitable for all patients. Also very few units in India and other developing countries have sufficient experience in their use.

Tissue oxygenation is commonly assessed by measuring arterial lactate levels, $ScvO_2$ or mixed venous oxygen saturation ($S\dot{v}O_2$) (Table 4). All these three are global indirect measures of tissue oxygenation. Decreased $ScvO_2$, $S\dot{v}O_2$ levels point to increased oxygen extraction by tissues experiencing an oxygen deficit. Increased lactate levels signify anaerobic metabolism because of insufficient oxygen supply to satisfy tissue requirements. The $S\dot{v}O_2$ requires the use of a pulmonary artery catheter (PAC). However, the $ScvO_2$ is generally regarded as a reliable substitute for the $S\dot{v}O_2$. The outcome impact of the PAC in hemodynamic stabilization has been controversial. Studies and these include meta-analysis have revealed conflicting outcomes—decreased morbidity, improved mortality following surgery, no benefit in the ICU, increased mortality associated with the use of the PAC.[30]

In a study on patients with established acute lung injury (ALI), PAC and central venous catheter (CVC) directed therapy revealed no differences in outcomes such as mortality, ICU free days and the number of ventilator free days.[31] Currently the SSC guidelines indicate that the $S\dot{v}O_2$ and $ScvO_2$ are equivalent for monitoring resuscitation.[23] The routine monitoring of patients with the PAC in patients with septic shock is not recommended. Yet many units use the PAC for guidance in the management of very critically ill septic patients who require large volume infusions, large doses of vasopressors and/or inotropes, particularly in the presence of ARDS. Management of patients in whom severe sepsis is complicated by cardiogenic shock or is associated with severe sepsis induced myocardial dysfunction, or is combined with hemorrhagic shock is also helped by the use of the PAC. In the above mentioned seriously complicated situations, the PAC allows a detailed hemodynamic analysis, allowing a measurement of the CI, stroke volume, stroke work index, pulmonary artery pressure, PCWP, systemic and pulmonary vascular resistances, DO_2 and $\dot{V}O_2$. It helps the intensivist to adjust these variables through appropriate therapeutic interventions aimed at improving tissue perfusion and supplying adequate oxygen for tissue needs. In conclusion, though the PAC is not indicated for use in every patient with septic shock, in special situations and in selected patients it may help better management, notwithstanding the statistical evidence quoted against its use.

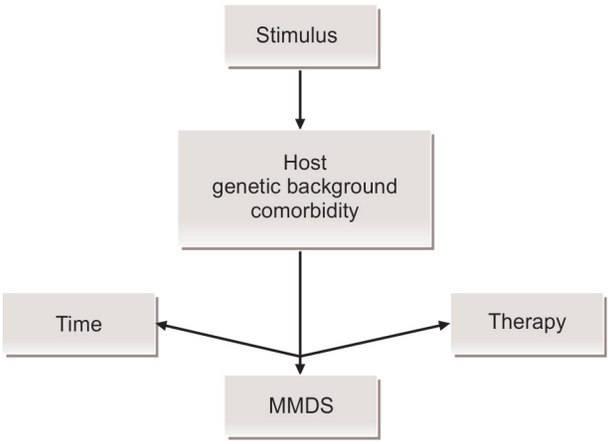
Outcome of EGDT in Severe Sepsis and Septic Shock

The genesis of EGDT and its proven outcome benefit arose from the seminal study by Rivers and colleagues.[22] Participants in the study by Rivers and colleagues were randomly assigned to receive goal-directed or standard resuscitation therapy. Patients in the goal-directed therapy group were resuscitated according to the EGDT protocol for at least 6 hours following arrival in the ED. In-hospital, 28 days and 60 days mortality rates for patients in the EGDT group were 30.5%, 31.3% and 44.3% respectively compared with 40%, 49.2% and 50.94% in the standard therapy group.[22] In addition, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, Simplified Acute Physiology Scores (SAPS) , multiple organ dysfunction scores were significantly better in the EGDT group 7–72 hours after protocol entry. An analysis of the literature by Otero and colleagues.[32] showed that these outcomes are reproducible, generalizable and have external validity. The importance of early recognition of sepsis and septic shock is self evident, as rapid and appropriate treatment benefit outcome.

MICROCIRCULATORY MITOCHONDRIAL DYSFUNCTION SYNDROME[33]

Death in septic shock is due to increasing tissue hypoxia leading to multiorgan dysfunction and failure. The question

Flowchart 4: Microcirculatory mitochondrial dysfunction syndrome (MMDS)



Source: Adapted from Spronk P, Kanoore-Edul V, Ince C. Microcirculatory and mitochondrial distress syndrome (MMDS): a new look at sepsis. In: Pinsky MR, Payen D (Eds). Functional Hemodynamic Monitoring, Update in Intensive Care and Emergency Medicine. Germany: Springer; 2005. pp. 47-67.

arises as to why in spite of goal directed therapy restoring hemodynamic stability, patients with septic shock still have a significant mortality. Current thoughts in many centers are directed to the MMDS (Flowchart 4) where DO_2 is more than adequate but oxygen does not reach the tissue cells, because of abnormalities in the microcirculation. Abnormalities in microcirculation include capillary spasm, capillary thrombi, a reduced capillary bed, poor blood flow in capillaries, increased permeability leading to edema, shunting of blood within small arterioles directly to the veins so that blood bypasses tissue cells. Impaired mitochondrial function prevents oxygen that reaches tissues from being utilized by tissue cells. As mentioned in Chapter Overview of Shock Syndromes, mitochondrial dysfunction may be due to oxygen deprivation caused by microcirculatory dysfunction, or may occur independently of disturbances in the microcirculation. Mitochondrial function could be adversely affected by the direct action on cell metabolism by cytokines and other noxious stimuli.

The microcirculatory mitochondrial dysfunction syndrome is being particularly researched upon in septic shock. Measures to determine abnormalities in microcirculatory flow have been touched upon in Chapter Overview of Shock Syndromes. A persistent increase in serum lactate and reduced $\dot{V}O_2$ in spite of normal or even more than normal DO_2 lends suspicion to the diagnosis of MMDS. Measures to counter this syndrome are being studied. These include further volume infusions—to further increase DO_2, a titrated infusion of nitroglycerine to increase microcirculatory blood flow and counter capillary spasm, provided there is no existing hypotension. Multiple action therapy in the form of fluid resuscitation plus vasoactive and inotropic support is reported to be effective in recruiting the microcirculation. The use of a NO donor agent can open the microcirculation thereby perfusing weak microcirculatory units. Also conceivably the use of an inducible nitric oxide synthase (INOS) inhibitor can reduce pathological shunting and recruit poorly functioning microcirculatory units. Whether the measures stated above are likely to help outcome is yet unknown.

Stabilizing the Airway and Breathing

Stabilizing the airway and breathing has been mentioned as an early prime concern in a patient admitted with severe sepsis and septic shock. If these basic functions are in question—due to excessive airway secretions, very low O_2 saturation, respiratory distress or an evolving ARDS, ventilator support should be prompt. ARDS usually develops later in the natural history of septic shock but may well be the first manifestation of severe sepsis. Ventilator support should follow the now clearly accepted lung protection strategies using relatively low tidal volumes (6 mL/kg of predicted body weight) with the upper limit of the plateau pressure being not more than 30 cm H_2O. Permissive hypercapnia may be allowed to minimize tidal volumes and plateau pressures (see Chapter Acute Lung Injury and Acute Respiratory Distress Syndrome).

Antibiotic Therapy

A number of studies have demonstrated the crucial importance of early administration of appropriate broad-spectrum antibiotics in reducing mortality in septic shock.[34-36] Kumar and colleagues[37] in a retrospective cohort study in patients with septic shock showed that increasing delay in the initiation of antimicrobial therapy after the onset of hypotension was associated with an increasing risk for death. These workers also showed that the median time to initiation of antibiotic therapy was a reliable and significant predictor of mortality. The recent SCC guidelines recommend starting IV antibiotic therapy as early as possible (within the first hour) as each hour's delay is associated with a progressive measurable increase in mortality.[23,34,37]

Antibiotic therapy should be prompt but as mentioned earlier should as far as possible be preceded by blood culture, culture of urine, Gram staining and culture of sputum, other body secretion (if indicated), wounds, bed sores, if present. Therapy should on no account await results of these tests. If cultures for any reason are delayed, antibiotic therapy should start forthwith.

The following features in relation to antibiotic therapy need consideration—

- The initial selection of an antibiotic or antibiotics against severe sepsis and septic shock should cover all likely pathogens and should take into consideration their ability to penetrate in adequate concentration the suspected source of sepsis.
- Patient factors such as pre-existing comorbid conditions, immune suppressed states, recent antibiotic administration, risk factors for multiple drug resistant (MDR) colonization, a history of drug allergies and intolerance play an important role in antibiotic selection.
- In case of nosocomial infections causing septic shock, a knowledge of the prevalence of various pathogens in the

hospital or in an ICU and the sensitivity of these organisms to antibiotics is another crucial factor in selection. (Also see Chapter Nosocomial Infections).

- There is a frighteningly increased prevalence of highly resistant Gram-negative infections in many critical care units in India. An increasing prevalence of resistant Gram-negative infections causing sepsis and septic shock is also being observed in the community. A combination of a carbapenam plus an aminoglycoside or a piperacillin-tazobactum with an aminoglycoside in full appropriate dosage would be justified to start with in severe sepsis or septic shock. In units with a very high prevalence of resistant pathogens like pan-resistant Pseudomonas aeruginosa or ESBL organisms, antibiotic treatment with alternative regimens such as colistin or polymyxin should be considered.
- Methicillin resistant staphylococcal infections are comparatively rare in most critical care units in India. If suspected, vancomycin or linezolid should be added to the antibiotic regime. The latter would also help to cover vancomycin resistant enterococci. Fulminant sepsis or sepsis where Gram-positive infection is possible or suspect, requires the use of a Gram-positive cover in addition to a Gram-negative cover.
- Severe sepsis and septic shock due to a community acquired pneumonia should be covered with amoxicillin or amoxicillin-clavulanate in addition to antibiotics that cover other likely organisms. The incidence of penicillin-resistant pneumococcal infection is low in India.
- In areas with a high prevalence of Candida species or in situations where fungal infection seems likely (as in neutropenia or immunocompromised patients) fluconozole, or echinocandins to cover fluconazole resistant *Candida glabrata* or *C. krusei* should be included in the antimicrobial regime.
- In neutropenic patients with sepsis or septic shock, a powerful combination of antibiotics is mandatory, e.g. piperacillin-tazobactum plus an aminoglycoside. Vancomycin may need to be added if there is a possibility of a staphylococcal infection. If there is no improvement and if fever persists over 24 hours amphotericin B or fluconazole is added to cover a fungal infection. This blunderbuss therapy in neutropenic patients with severe sepsis or septic shock of unknown etiology is unfortunate but usually unavoidable.[38]
- The possibility of fulminant disseminated hematogenous tuberculosis causing the picture of severe sepsis and septic shock in immunocompromised patients and rarely even in immunocompetent patients should always be kept in mind in our country and in other poor countries where tuberculosis is rampant.
- In tropical countries, fulminant *P. falciparum* infections, leptospiral infections, rickettsial infections and dengue can result in severe sepsis and MOF. If source of infection is not apparent, and if the clinical picture is compatible with any one of the above diseases, appropriate treatment is specifically given, even if convincing proof of these disease is not present.
- Observational studies indicate that outcome of sepsis[35] and septic shock is worse if the causative microorganisms are not sensitive to the initial antibiotic regimen. The importance of hitting early and hitting hard cannot be over emphasized.

How Long Should Antibiotics Be Given in Severe Sepsis or Septic Shock?

- Once the causative organism is identified on culture and the microbial sensitivity to antibiotics is available, further antibiotic therapy should be directed solely against the identified pathogen. Unnecessary antibiotics should be promptly discontinued to avoid nosocomial superinfections, fungal infections and drug toxicity. The single most effective antibiotic as judged from minimum inhibitory concentration (MIC) results suffices. Most units however still prefer to treat *P. pyocyaneus* infection and perhaps even klebsiella infection with a combination of antibiotics though evidence for this approach has been disputed.
- The de-escalation of antibiotics in patients who have severe sepsis or septic shock has been shown to result in better outcomes.[39] Current recommendations are to continue therapy for 7–10 days.[41] Longer duration may be justified in patients who respond slowly in severe *P. pyocyaneus* infection, in neutropenic patients and in patients with immunologic deficiencies.
- It is unfortunate but true that in many patients with severe sepsis and septic shock, cultures are negative. The decision to continue, taper, stop antibiotic therapy depends on overall clinical assessment of the patients.

If in patients with the clinical picture of severe sepsis or septic shock, the source of sepsis is underdetermined, it is important to look for noninfectious etiologies known to give rise to a similar clinical picture. These include acute pancreatitis, multiple blood transfusions, poisoning, severe vasculitis, acute connective tissue disorders, thrombotic thrombocytopenic purpura, cholesterol embolic syndrome and the hemophagocytic syndrome.

Identifying the Source of Infection and Source Control

After sending the requisite cultures and then starting an empirical antibiotic regime, an intensive search for possible sources of infection should be made. This should include an extremely thorough clinical examination, laboratory tests, and the use of current imaging techniques. Any localized collection of pus within the body should be promptly drained. Intra-abdominal abscess, an empyema of the gall bladder, paracolic abscess, pelvic abscess, an appendicular abscess, an empyema tucked away in the paravertebral space are some localized collections of pus that should be avidly searched for (Box 4). The common sources of infection are the chest and

Box 4: Common sources of severe sepsis/septic shock requiring urgent source control

- Pneumonia, Empyema
- Intra-abdominal abscess
- Gangrenous cholecystitis
- Necrotizing pancreatitis with infection
- Ascending cholangitis
- Amebic liver abscess
- Perforated viscus
- Ischemic bowel
- Obstructive uropathy
- Complicated pyelonephritis or perinephric abscess
- Necrotizing soft tissue infections (necrotizing fasciitis)
- Clostridial myonecrosis
- Iatrogenically induced sepsis

Note: In the tropics and poor developing countries—sources include falciparum malaria, dengue, leptospiral infection, and amebic infection.

the abdomen. Investigations should therefore always include a CT scan of the chest, abdomen and the pelvis. No amount of antibiotics can salvage a situation if a localized abscess is left undrained—the sooner it is drained the better. The possibility of iatrogenic hematogenous sepsis arising from contaminated central lines should always be kept in mind. Suspect central lines should be removed and the tips sent for culture. Cultures from central and peripheral lines should always be done. Laboratory tests for tropical infections listed earlier should be done as and when necessary.

In close to 30% of patients, no source of infection can be definitely identified. The frequency of positive blood cultures varies with different clinical situations, and with different microbiological laboratories. In our set-up, the incidence of positive blood cultures is about 30%. Again patients who have already received, or are receiving antibiotics, are less likely to have positive cultures. It is to be remembered that death from septic shock can result from an undetected focus of sepsis or from a focus of sepsis which for many reasons need not yield positive blood cultures—this is particularly true in patients with abdominal sepsis.

Difficulties in the diagnosis and location of a source of sepsis may be immense in critically ill individuals, particularly if modern diagnostic and imaging facilities are unavailable, as is to be expected in many third world countries. These difficulties need special emphasis in the following situations.

In Pregnancy and Parturition During pregnancy and soon after delivery the source of sepsis can be easily missed. An acute appendicular abscess in a patient with advanced pregnancy often produces discomfort in the right hypochondrium, and in the tropics can be mistaken for an amoebic hepatitis or cholecystitis. A pelvic abscess can also be easily missed during pregnancy if not specifically looked for. Diagnosis is doubly difficult because of constraints on imaging procedures.

Perforation of the gut due to any etiology soon after a caesarean delivery, is a disaster which is often missed. The subject has been discussed under Intra-abdominal Sepsis in the Section Surgical Infections in the Intensive Care Unit.

In the Aged and the Infirm Problems of identifying the source of sepsis in the aged are invariably extremely difficult. The body responses to sepsis are blunted, and this is one reason why the diagnosis is delayed. Localizing signs are few and sometimes ill-defined and indeterminate. For example, perforation of the large bowel may produce very few signs, and may therefore be missed till too late. Pneumonia or an empyema tucked away in the paravertebral space may also remain undiagnosed for a period of time in the old and the infirm.

In Neutropenic and Immunocompromised Patients The problems in these patients are often impossibly difficult. In fact, neutropenic patients with sepsis, often have no identifiable source of infection. In these patients, the source of infection is believed to be a small or even microscopic focus in the bowel or perhaps in some other organ system.

Late Stage (Preferably Termed the Later Stage) of Sepsis

The late stage (preferably termed the later stage) of sepsis commences after the first 6 hours are over. The late stage merits what is sometimes termed a second line treatment in contrast to the first line treatment already described during the first 6 golden hours. Unquestionably it is the first line treatment in the early stage which chiefly influences outcome. Even after the first 6 hours it is vital to continue to maintain hemodynamic stability and maintain tissue perfusion so as to counter tissue hypoxia. This might entail titrated volume replacement as also vasopressor and/or inotropic support for several hours and in some patients for several days.

Ventilator Support

Almost all patients with severe sepsis and septic shock need more than just supplemental oxygen. They need ventilator support—some may need this in the early phase or stage, others often require it later. These patients generally have a low partial pressure of oxygen (PaO_2) because of ventilation-perfusion inequalities within the lung, and in hemodynamically unstable patients because of a low partial pressure of oxygen in mixed venous blood (PvO_2) which contributes to a low PaO_2. Even otherwise, these patients are generally tachypneic with respiratory rates ranging from 30–45 breaths/minute. Ventilator support rests the muscles of respiration, sharply lowers the oxygen cost of breathing, enabling more oxygen to be delivered to the vital organs of the body. ARDS is an important complication of sepsis necessitating ventilator support using lung protective measures (see Chapter Acute Lung Injury and Acute Respiratory Distress Syndrome).

Support to Other Organ Systems

Septic shock often leads to multiorgan failure. Each organ system requires adequate support. Renal replacement therapy to counter acute renal failure is often necessary and

should not be unduly delayed. The mortality in patients with more than three organ failure is horrendous in several bacterial sepsis but is not so forbidding in severe sepsis due to tropical infections.[41]

Use of Recombinant Human Activated Protein C in Severe Sepsis

Activated Protein C (APC) has now been shown to be of no use in severe sepsis and septic shock. The drug has been withdrawn from the market and is no longer available.

The story of APC is indeed a blow to evidence based medicine and for that alone it needs to be briefly reported. In 2001, after the Prowess Trial[40] this drug was acclaimed as the one and only drug which had a direct salutary action on severe sepsis and septic shock. The medical profession was exhorted to use it. Then came the Enhance Trial and the Address Trial,[42] the latter noting an increase in mortality in patients with sepsis who had a single organ failure and who were administered this drug. Following this, came the Surviving Sepsis Guidelines (2008) which advocated its use only in patients with severe sepsis with a high APACHE score (>25) and multiorgan failure. And then at last came the recent Prowess Shock trial and the latest 2011 Cochrane Database System Review.[43] This review included in its database a review of five randomized control trials involving 5,101 participants. The review reported that APC did not reduce the risk of death in adult participants with severe sepsis and therefore should not be used in treating patients with severe sepsis and septic shock. Additionally APC was associated with a higher risk of bleeding. They concluded, "unless additional randomized controlled trials (RCT) provide evidence of a good treatment effect, policy makers, clinicians and academicians should not promote the use of APC". At last, the story of APC which in 2001 began with a bang ended in 2012 with a whimper!! Perhaps this review may lead to further debate, and (who knows!) even more RCTs with further questionable results—an example of evidence based medicine enjoying an internecine quarrel!

Use of Corticosteroids

There have been a number of trials and a number of reports with conflicting evidence with regard to the use of corticosteroids in severe sepsis and septic shock—a state of affairs confusing and disturbing to the intensivist engaged in the management of this critical problem. Among the various studies is the Corticus Study group—Hydrocortisone therapy for patients with septic shock.[44] This study concluded that hydrocortisone did not improve survival or show reversal of shock in patients with septic shock or in patients who did not have a response to adrenocorticotropic hormone (ACTH). Current recommendations[23] suggest that hydrocortisone should not be used to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. In case this is not achievable, IV hydrocortisone in a dose of 200 mg/day can be used. When used, the risk of superinfection should limit its use preferably to not more than 7 days. However, corticosteroids should not be administered for the treatment of sepsis in the absence of shock.

What does one do in clinical practice? To use, or not to use—that is the question! Evidence seems to change again and again. Even so, and in spite of current evidence, there will probably be as many using this drug as those not using it!

Perhaps hydrocortisone in small doses of 50 mg 6–8 hourly may have a role in early shock, in those patients who remain hypotensive despite a volume load and the use of vasopressors.[44].

Blood Product Administration

- The recent surviving sepsis guidelines recommend that RBC transfusions should be given only when hemoglobin (Hb) falls less than 7 g/dL so as to target a Hb of 7–9 g/dL. This recommendation is based on Transfusion Requirements in Critical Care Trial which suggested that a Hb of 7–9 g/dL when compared to 10–12 g/dL was not associated with an increased mortality in adults.[45] This trial suggests that red blood cell transfusion in sepsis increases oxygen delivery but does not necessarily increase oxygen consumption.[46-48] Not withstanding evidence (which of course could change!) this recommendation goes against clinical judgment. For one, it goes against the goal directed resuscitative protocol that advises a PCV of 30 % in patients with a low $ScvO_2$; for another it is impossible to predict blood flow and DO_2 to vital organs such as the heart, the brain, the kidneys and the gut in critically ill individuals. Nor is it possible to predict the extent and degree of vessel wall disease particularly in severely ill elderly individuals. It is a well accepted fact that myocardial ischemia and/or a poor cerebrovascular circulation can exist without being clinically manifest. For example, critically ill patients with well-marked coronary artery disease may have a normal ECG tracing. An increase in oxygen content should benefit such patients. Whatever the present evidence, there are many who would aim at an Hb close to 10 g/dL.
- Fresh frozen plasma should not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures.[23]
- The guidelines for the SCC[23] recommend that platelets should be prophylactically transfused only in patients with severe sepsis when counts are less than 10,000/mm^3 in the absence of apparent bleeding, and also when counts are less than 20,000/mm^3 if the patient has a significant risk of bleeding. Higher platelet counts greater than or equal to 50,000/mm^3 are advised for active bleeding, surgery, or invasive procedures. Major surgical procedures require platelets of more than 100,000/mm^3.

METABOLIC SUPPORT

Glycemic Control

A randomized multicentric trial in cardiac surgery patients compared a conservative glycemic control to a tight glycemic control (blood sugar <120 mg/dL) through the use of IV insulin.[49] Patients who had tight glycemic control had a significant reduction in morbidity and mortality at the end of 1-year vis-à-vis patients who were offered the usual conservative control. Other advantages of tight control were a reduced intensive care stay, a reduced incidence of renal failure and of critical illness polyneuropathy.[49] However, a recent study by the same group in medical critically ill patients showed no significant difference.[50] In view of the danger of hypoglycemia particularly in developing countries where nursing supervision and resources are limited, it is much safer to use a titrated dose of insulin so as to keep the blood glucose levels around 150 mg/dL.

Use of Bicarbonate

The use of bicarbonate in the treatment of sepsis induced lactic acidosis is controversial.[51,52] In fact, there is no evidence to support its use.[51] However, in the presence of severe acidosis with a pH of less than 7.15, IV bicarbonate is used by many units. Possibly its use is unlikely to improve the ultimate outcome. At times the use of bicarbonate in patients with a low pH has a salutary effect on myocardial function and blood pressure.

The use of bicarbonate can have adverse effects. The release of CO_2 following its use can cause an intracellular acidosis; detrimental to cell function. It can also lead to a fall in the ionized calcium which theoretically could reduce myocardial contractility. Repeated use of IV bicarbonate can result in an acute volume overload. Adverse effects of bicarbonate can be reduced by using slow IV infusions instead of rapidly administered boluses. In summary, sepsis induced lactic acidosis is best corrected by improving the underlying primary disorders by measures outlined earlier.

Nutritional Support

This is vital for survival in the hypercatabolic state that characterizes sepsis and septic shock. Hyperalimentation is frequently necessary if the gut function is poor and does not allow adequate intake of calories, proteins, carbohydrates, minerals and vitamins (see Chapter Nutrition Support in the Critically Ill Adult).

Prophylaxis for Deep Vein Thrombosis and Stress Ulcers

Patients with severe sepsis need prophylaxis against deep vein thrombosis either with low molecular weight heparin, or if this is inappropriate, with the use of a mechanical protective device (intermittent compression device or compression stockings). Prophylaxis for stress ulcers in severe sepsis is provided by the use of H_2 receptor-antagonists or proton pump inhibitors. Patients without risk factors do not need prophylaxis.[23] Most intensivists prefer the use of sucralfate. If a GI bleed has already occurred or if the patient is at high risk for a GI bleed, use of a proton pump inhibitor is advocated.

Immunotherapy—Neutralization of Toxic Mediators, Cytokines, in Sepsis

Septic shock is mediated by numerous interacting endogenously produced mediators and cytokines, triggered by the action of bacterial toxins, chiefly endotoxins derived from Gram-negative bacteria. A search is on for pharmaceutical agents that can directly counter these harmful endogenous mediators, or their noxious effects on tissues. Agents tried include nonsteroidal anti-inflammatory drugs, nalaxone, pentoxiphylline, antitumour necrosis factor, surfactant (to replace depleted surfactant in ARDS). The use of antibodies against proinflammatory ILs or of monoclonal antibodies to the core antigen of the J-5 strain of *E. coli* has yielded unsatisfactory results. High dose corticosteroids and the use of a number of agents to inhibit activity of nitric oxide synthetase have proved futile. It is unlikely that a single inhibitor or antagonist to the numerous interacting mediators in severe sepsis is ever likely to succeed. Perhaps a multipronged attack on the important proinflammatory cytokines and mediators that inflict damage on the host seems a more rational approach.

PROBLEMS IN MANAGING SEVERE SEPSIS AND SEPTIC SHOCK IN INDIA AND OTHER DEVELOPING COUNTRIES

The major problem is the very late admission of patients with severe sepsis to the ED or the ICU. Patients admitted often have advanced multiorgan failure with refractory hypotension. They have reached a point of no return. The reason for the delay is a lack of awareness of the clinical features of sepsis and severe sepsis among general practitioners and the lack of urgency among doctors in hospitals who look after these patients. Continuing medical education is the only answer to mitigate this problem.

Another problem is the poverty of resources and of trained personnel in ICUs outside the larger metropolitan centers of poor countries. To a lesser extent this problem is also valid in the larger cities of India and other poor countries. Lack of resources includes absence of modern microbiological, imaging and monetary facilities and the unavailability in many units in the country of powerful antibiotics to counter infection. Lack of resources should also include lack of information technology in poor countries, or lack of awareness of the importance of its use.

The problems in the management of severe sepsis and septic shock in rural and semi-rural India where hospitals are poorly staffed and equipped can be impossibly difficult.

Box 5: Sepsis Bundle for poor tropical countries having poorly equipped ICUs

- Awareness and clinical recognition
- Basic laboratory tests—CBC, urine, relevant cultures, HIV rapid test, malaria- thick and thin smears, IgM dengue, tests for other tropical infections (before starting antimicrobials)
- Fluid resuscitation followed wherever necessary by vasopressors and inotropes
- Assessment of end-points (treatment response)—
  - CVP of 8–12 mm Hg
  - Urine output ≥0.5 mL/kg/hour
  - Blood pressure (MAP ≥65–70 mm Hg)
  - Skin perfusion (improved with better capillary refill)
  - Tests for different organ functions should be normal or show improvement
- Antimicrobials—antibiotics, antimalarials , others (depending on the locale and clinical features—to be started within the first hour)
- Source identification and control

Box 6: Programming priorities for sepsis in poor countries

- Education
- Laboratory facilities
- Developing sepsis management guidelines in hospitals with limited resources
- Simple diagnostic tests to identify end-points of resuscitation
- Antimicrobials (antibiotics, antimalarials etc) – their appropriate and prompt use.
- Improving critical care facilities
- Use of information technology to help in treatment

Box 5 suggests the sepsis bundle for poor tropical countries in hospitals with meagre facilities and resources.

Box 6 suggests programming priorities for the management of severe sepsis in poor countries.

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CHAPTER 17

Cardiac Compressive Shock

INTRODUCTION

Compression of the heart and the great veins opening into the right heart can restrict and sharply reduce diastolic filling of the ventricles. This results in a low output state with inadequate tissue perfusion akin to the picture of cardiogenic shock. The classical cause of acute cardiac compression resulting in shock is cardiac tamponade due to accumulation of fluid within the pericardial sac. This chapter is devoted to the description of cardiac tamponade. Before we give the description, it should be noted that acute severe cardiac compression resulting in a shock-like low output state can also result from a tension pneumothorax. The problems here are further compounded by disturbances in pulmonary function and respiratory exchange due to acute compression collapse of one lung, with a marked shift of the mediastinum to the opposite side and by mediastinal flutter during inspiration and expiration. Acute cardiac compression can also occur in mechanical ventilation with positive end-expiratory pressure (PEEP). In the presence of very high intrathoracic pressure, the large veins opening into the right heart and the heart chambers are sufficiently compressed to sharply restrict diastolic filling and produce a low output state. A major contributory factor in this situation is the strain imposed on the right ventricle by increased vascular resistance within the pulmonary capillaries, and perhaps a further impairment of filling of the left ventricle by a septal shift that encroaches on the left ventricular volume.

CARDIAC TAMPONADE[1,2]

General Considerations

The pericardium has very little elasticity when acutely stretched. Therefore, a very rapid accumulation, as little as 300–500 mL of fluid within the pericardial sac can result in a sharp rise in the intrapericardial pressure, and cause compression or tamponade of the chambers of the heart. Fluid with a higher specific gravity, like blood or thick pus, will cause greater compression and greater tamponade. As little as 300 mL of thick pus formed acutely within the pericardial sac can lead to death from tamponade in children. On the other hand, a slow accumulation of fluid within the pericardial sac allows the pericardium to stretch maximally so that intrapericardial pressure may not be sufficiently raised to produce a serious tamponade even with an effusion of one liter or more.

Cardiac tamponade can result from pericardial effusions due to any cause. The important medical causes include acute viral (idiopathic) pericarditis, pericarditis secondary to metastatic neoplastic disease, uremic pericarditis, purulent pericarditis, tuberculous pericarditis, pericarditis occurring in patients with myocardial infarction who have been anticoagulated, and occasionally in systemic lupus erythematosis. In tropical countries, a left lobe amebic liver abscess rupturing into the pericardium, is a rare but important cause of tamponade.

In an emergency setting, unquestionably the most important cause is hemopericardium resulting from trauma and accidents. A dissection of the aorta which ruptures into the pericardial sac can also result in immediate tamponade and quick death.

In the intensive care unit, postoperative bleeding following open heart or cardiothoracic surgery, and hemopericardium in sepsis and septic shock are important causes.

Diagnostic and therapeutic procedures performed in a critical care unit can sometimes be complicated by acute cardiac tamponade. Perforation of the right atrium by a central venous line, particularly when the line is used to administer fluids or is used for parenteral alimentation, is an important

Box 1: Iatrogenic causes of cardiac tamponade

- Postoperative hemorrhage following cardiac surgery
- Use of anticoagulants
- Barotrauma during mechanical ventilation
- Upper gastrointestinal (GI) endoscopy or sclerotherapy resulting in esophageal perforation
- Internal jugular or subclavian vein puncture
- Perforation of the heart by indwelling catheter (used for hemodynamic monitoring, pacing), or during angiography
- Perforation of the heart or coronary artery during balloon angioplasty

cause of acute cardiac tamponade. Perforation of the heart by a pacing catheter, or tear of the coronary artery during balloon angioplasty, or of the heart by catheters used for balloon valvuloplasty, can all cause hemopericardium, resulting in cardiac tamponade and death (Box 1).

Pathophysiology[1,3]

A rapid accumulation of fluid within the pericardial sac leads to an acute increase in intrapericardial pressure. When this intrapericardial pressure rises to equal the atrial and the right ventricular diastolic pressure, the transmural pressure distending these chambers declines to about zero. A further accumulation of pericardial fluid leads to a further increase in the intrapericardial pressure and the right ventricular diastolic pressure, so that they now equal the left ventricular diastolic pressure. Cardiac tamponade thus occurs on equalization of the intrapericardial and ventricular filling pressures. This results in a marked fall in the distending pressure and therefore in the diastolic volumes of both ventricles, resulting in a fall in the stroke volume. The reduction in stroke volume is initially compensated for by an increased adrenergic drive that causes tachycardia and an increase in the ejection fraction. To a lesser extent, it is also compensated for by an increase in circulatory volume due to salt and water retention induced by a decreased urinary excretion of sodium. A fall in sodium excretion is related to the reflex inhibition of the release of the atrial natriuretic factor produced by a rise in intrapericardial pressure. With severe cardiac tamponade, the compensatory mechanisms do not suffice to prevent a sharp fall in cardiac output and in the systemic blood pressure, so that perfusion of vital organs is impaired. Reduced coronary perfusion results in subendocardial ischemia. Sinus tachycardia is usually present, but sinus bradycardia may also occur through a reflex mediated by the cardiac depressor branches of the vagus nerve or through nonvagal mechanisms. Severe bradyrhythms foreshadow electromechanical dissociation and death in patients who are almost pressureless because of severe tamponade.

Hemodynamic Profile[1]

The hemodynamic profile in cardiac tamponade is characterized by a marked rise in the central venous and right atrial pressure, and by equalization of the right atrial, right ventricular diastolic and the pulmonary capillary wedge pressures (PCWP). The PCWP is an index of the left ventricular diastolic pressure. If the intrapericardial pressure were to be measured, it would be found to be equivalent to the right atrial pressure, the right ventricular diastolic pressure and the PCWP. Tachycardia, hypotension and a raised systemic vascular resistance with poor tissue perfusion characterize the clinical hemodynamic profile.

It should be noted that the rise in the right atrial (and intrapericardial) pressure is less marked in the presence of hypovolemia, so that cardiac tamponade unless very severe, may be masked in hypovolemic states.

Another point of note is that if the left ventricular diastolic pressure is elevated to start with because of left ventricular disease, then cardiac tamponade occurs when the intrapericardial, right atrial and right ventricular diastolic pressures become equal, but these pressures will be lower than the left ventricular diastolic pressure as gauged by the PCWP.

Clinical Features[2,4]

The clinical features of acute cardiac tamponade are—

- A progressive rise in the central venous pressure (CVP) as gauged by a clinical estimation of the jugular venous pressure, to +15 to +20 mm Hg. When hypovolemia is associated with cardiac tamponade (as after trauma or accidental injuries), the CVP may not show the degree of rise normally expected. Such a low pressure tamponade may pose difficulties in diagnosis. The liver is not usually enlarged in acute cardiac tamponade.
- A falling arterial pressure. There is a progressive fall (initially in the systolic pressure), with an increasing inadequacy in tissue perfusion. This is characterized by oliguria, cold, sweating peripheries, restlessness, together with all the features of a rapidly evolving shock state.
- A small quiet heart. The apex is not felt and the heart sounds are faint or inaudible. Clearly audible sounds do not however negate the diagnosis of cardiac tamponade.
- A pulsus paradoxus. The volume of the pulse falls perceptibly during inspiration and increases during expiration and this can be best elicited by a sphygmomanometer. The cuff pressure is raised well above the systolic pressure, and is then very slowly lowered till Korotkoff's sounds are first heard only in expiration. The cuff is slowly further deflated so that the sounds are equally well heard both during inspiration and expiration. The difference between these pressures gives the magnitude of pulsus paradoxus; it exceeds 10 mm Hg in cardiac tamponade.

Complete disappearance of the pulse on inspiration can occur in severe tamponade. A pulsus paradoxus on palpation is often better appreciated in the carotids or femorals rather than in the radials, particularly when the volume of the pulse is low. At times, a pulsus paradoxus not appreciated clinically or with a sphygmomanometer can be demonstrated on recording the arterial pressure via an intra-arterial cannula. The degree of paradoxus in the arterial pulse is often significantly greater

in direct arterial pressure recordings as compared with a clinical estimation using the sphygmomanometer.

A pulsus paradoxus in cardiac tamponade is merely an exaggeration of the normal physiology during inspiration which is characterized by a slight decrease in the left ventricular stroke volume and in the systolic arterial pressure. In cardiac tamponade, inspiration causes a decrease in the intrapericardial and right atrial pressures, with increased blood flow to the right ventricle. This increase in venous flow to the right ventricle during inspiration results in an increase in the dimensions and size of the right ventricle, the septum being straightened and pushed to the left. There is a resulting decrease in the left ventricular volume and size, with decrease in left atrial and left ventricular diastolic pressures. This leads to a fall in aortic flow and in systolic arterial pressure. Pulsus paradoxus in cardiac tamponade is thus chiefly related to increased inspiratory venous return and increasing flow into the right ventricle. Inspiratory pooling of blood within the lungs may result in a reduced gradient between the pulmonary venous circulation and the left heart, and this may be a minor contributory factor toward the observed inspiratory fall in left ventricular stroke volume and systolic arterial pressure.

- Tachycardia with a feeble pulse volume is invariably present. Bradycardia is often a preterminal event and precedes electromechanical dissociation and death.
- Inspiratory swelling of the neck veins may be noted. Cardiac dullness may be increased on percussion, if there is a sufficiently large collection of fluid in the pericardial sac.
- Patients with acute cardiac tamponade are tachypneic, restless, in shock, and may complain of precordial discomfort. A pericardial or a pleuropericardial rub may be heard. If hypotension is marked, the patient is generally obtunded.

Diagnosis[2,5] (Box 2)

A well-marked rise in the CVP is a requisite for the diagnosis of cardiac tamponade, except in rare instances where hypovolemia is associated with tamponade. In the latter situation, diagnosis is difficult and can only be arrived at if the background factors (trauma, injury) are kept in mind, and further relevant investigations done. It is important to recognize cardiac tamponade at a point in time when the chief physical finding is a rising CVP. A rise in CVP to +15 mm Hg in the presence of a moderate sized pericardial effusion suffices for a diagnosis of cardiac tamponade. The diagnosis can be made with a lesser degree of rise in CVP if pulsus paradoxus above 10 mm Hg is present or if the atrial and the right- and left-sided diastolic filling pressures are equalized. It is obviously unwise to wait for a falling blood pressure before making a correct diagnosis. Unfortunately, a rise in the CVP in a critical care setting can be due to several factors, notably over-infusion of intravenous fluids and myocardial dysfunction.

Acute right heart failure, due to right ventricular infarction, or massive pulmonary embolism may on clinical examination mimic acute cardiac tamponade as these produce a rise in the CVP. Acute increase in the heart size with clear lung fields may further confuse the issue. However, the other clinical features of acute myocardial infarction and the presence of background features against which pulmonary embolism occurs should help in the diagnosis. Pulsus paradoxus in the presence of a rising CVP always points to cardiac tamponade. Pulsus paradoxus is not observed in acute congestive heart failure, but may rarely be observed with massive pulmonary embolism. Other conditions causing pulsus paradoxus include profound hemorrhagic shock, other forms of severe hypotension and obstructive lung disease.

The diagnosis of acute cardiac tamponade is frequently missed in acute bacterial pericarditis complicating acute pneumonias or sepsis. This is because a rapid accumulation of 250 mL of pus will demonstrate no clinical signs of fluid within the pericardial sac. A sudden clinical deterioration in a patient with lobar pneumonia or sepsis in the presence of a raised jugular venous pressure, should always suggest the correct diagnosis.

Box 2: Diagnosis of cardiac tamponade

Marked rise in CVP, tachycardia, hypotension
Pulsus paradoxus >10 mm Hg
Chest X-ray: rapidly increasing cardiac silhouette with clear lung fields; increasing size of mediastinum after open heart surgery
ECG: electrical alternans of P, QRS and T waves; sudden fall in voltage of tracing
Echocardiography: collapse of the right atrium and the right ventricle in diastole is a very sensitive sign of pericardial effusion causing hemodynamic compromise
Hemodynamic profile: raised atrial pressure; equalization of atrial, right and left ventricular diastolic pressures

Abbreviations: CVP, central venous pressure; ECG, electrocardiography.

Chest X-Ray

A normal heart size does not rule out cardiac tamponade. A rapidly increasing cardiac silhouette with clear lung fields is however a feature of cardiac tamponade. Following open heart surgery, the presence of hypotension, raised CVP, and enlarged mediastinal shadow on an X-ray of the chest, strongly suggest cardiac tamponade.

Electrocardiography

The electrocardiography (ECG) may show features of electrical alternans of P, QRS and T waves but this is not commonly observed. A sudden fall in voltage in the ECG tracing should also suggest the development of pericardial effusion. A myocardial rupture following infarction is often associated with a slow junctional rhythm, promptly followed by electromechanical dissociation.

Doppler Echocardiography[6]

Doppler echocardiography is the best diagnostic tool for the diagnosis of pericardial effusion and cardiac tamponade. Echocardiography not uncommonly underestimates the

quantity of fluid in the pericardial sac which is better revealed on a computed tomography (CT) or magnetic resonance imaging (MRI) study. The presence of tamponade is however best brought out by a Doppler echo which shows the following characteristic features—

- Circumferential pericardial fluid layer and compressed cardiac chambers with high ventricular ejection fractions.
- Doppler study shows marked respiratory variations in transvalvular flow; both atrial and ventricular septa move sharply leftward on inspiration, reversing on expiration.
- During early diastole the right ventricle wall collapses (invaginates) and in late diastole the right atrial wall invaginates. The ventricular wall collapse is a less sensitive but more specific finding; whereas right atrial wall collapse is more specific if the inward movement lasts more than 30% of the cardiac cycle.
- Left ventricular wall collapse usually occurs under specific conditions, as in patients with localized postsurgical tamponade.

These wall changes occur when respective chamber pressures temporarily fall below the pericardial pressure.

Hemodynamic Profile

In an intensive care setting, provided that time is available, a hemodynamic study would show a raised atrial pressure and equalization of the atrial, right ventricular diastolic and left ventricular diastolic pressures. Equalization should always be measured at the end-expiratory phase, and it should be noted that the equalization need not be exact or perfect, particularly if the PCWP or pulmonary artery end-diastolic pressure is used (as it invariably is) as a measure of the left ventricular diastolic pressure.

Variant Forms of Cardiac Tamponade[2]

- Low-pressure tamponade[7] occurs at diastolic pressure of 6–12 mm Hg and is chiefly observed in patients with hypovolemia , hemorrhage, or after a diuretic-induced volume depleted circulation. Patients are generally normotensive and pulsus paradoxus is absent; characteristic fluctuations in transvalvular diastolic Doppler flows are observed. A fluid challenge with a liter of warm saline can result in the typical tamponade dynamics.
- Hypertensive cardiac tamponade has all the classic features of tamponade but occurs at high arterial pressures (even often >200 mm Hg). It has been ascribed to an excessive alpha-adrenergic drive. There is invariably a history of hypertension present.
- Regional cardiac tamponade occurs when any area over the heart is compressed by a loculated effusion. This is observed especially after cardiac surgery and is more frequent after postoperative anticoagulant therapy. Postoperative myocardial stiffness, hemorrhage, and fluid electrolyte disturbances generally preclude the presence of classical signs such as pulsus paradoxus. Doppler echocardiography, a widened mediastinal shadow on imaging, hypotension, tachycardia and a raised CVP, all considered in their entirety allow diagnosis.
- After right ventricular infarction, a loculated effusion can cause selective right-heart tamponade in which right atrial pressure is higher than left atrial pressure. Diagnosis is difficult as there is no pulsus paradoxus.
- Effusoconstrictive pericarditis shows the hemodynamic changes of a cardiac tamponade. The changes persists (because of the underlying constriction) even after the pericardial fluid has been drained.

Management[1,2,5]

Pericardiocentesis[8]

Acute cardiac tamponade particularly when due to hemopericardium as a result of trauma or injury should be dealt with on an emergency basis. An immediate pericardiocentesis is mandatory. The technique of this procedure is described in a separate chapter.

Cardiac tamponade after open heart surgery necessitates re-surgery to remove blood clots and fluid causing tamponade. Most surgeons prefer to relieve tamponade from other causes by a surgical procedure, wherein a pericardial window is fashioned surgically and a drain left within the pericardial sac. The drain is removed when it stops draining. An antibiotic cover is generally necessary for a few days.

Supportive Treatment

Supportive treatment perhaps buys time. The use of inotropic support with or without vasodilator therapy (to reduce systemic vascular resistance) is controversial. Dobutamine is the preferred inotropic drug as it also has a vasodilator effect.

Volume infusions are also used to counter hypotension. They would help if there is hypovolemia but may be otherwise counterproductive as they could increase intracardiac pressure and heart size, which in turn would increase intrapericardial pressure thereby further reducing the transmural pressure supporting the circulation.

Supportive treatment is never a substitute for removal of the tamponade by drainage of the fluid compressing the chambers of the heart.

Mechanical ventilation with positive pressure breathing should be avoided in patients with tamponade because this further decreases cardiac output.[4]

It is important to keep a close clinical watch after pericardiocentesis has been done to determine if tamponade recurs. A rising CVP is again an ominous sign. If a Swan-Ganz catheter is *in situ*, demonstration of an equalization of the atrial, right ventricular diastolic and PCWP should point to a recurrence of the tamponade.

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CHAPTER 18

Anaphylactic Shock

GENERAL CONSIDERATIONS[1]

The incidence of anaphylactic shock in hospitalized patients is around 1 in 10,000, and the fatality rate is as high as 10–20%. Anaphylactic shock is an anamnestic response in which a sensitized individual comes in contact with an antigen. The antigen combines with specific immunoglobulin E (IgE) antibodies on mast cells and basophils, and induces the release of mediators such as histamine, platelet activating factor and other mediators that mediate the anaphylactic response. The latter is characterized by severe vasodilatation, bronchoconstriction, pruritus and increased vascular permeability. The common precipitating agents for anaphylaxis include drugs, particularly penicillin. Other antibiotics can also give rise to anaphylaxis. Contrast material and blood products are important causes of anaphylaxis. In fact, almost any and every drug including steroids has been shown to cause an acute anaphylactic reaction at one time or another.[2]

Anaphylactoid reactions are different from anaphylactic shock. The former are related to the direct release of mediators by the offending agent from mast cells and basophils without IgE antibodies coming into play. This direct release of mediators may be brought about by complement-mediated reactions or by nonimmunological activation of mast cells. Products of arachidonic acid breakdown include leukotrienes which increase vascular permeability and induce bronchoconstriction, as also thromboxanes and prostaglandins. Prostaglandin D2 can further cause bronchoconstriction. Common etiological agents that result in anaphylactic shock and anaphylactoid reactions are listed in Box 1.

Box 1: Commonly used agents implicated in anaphylactic and anaphylactoid reactions

- Antibiotics—
  - Penicillin and analogs
  - Sulfonamides
  - Tetracyclines
  - Streptomycin
- Local anesthetics—
  - Lidocaine
- General anesthetics and muscle relaxants—
  - Thiopental
  - Tubocurarine
- Non-steroidal anti-inflammatory agents
- Blood products and vaccines—
  - Red blood cell, white blood cell and platelet transfusions
  - Gamma globulin
  - Rabies vaccine
  - Tetanus antitoxin, toxoid
  - Diphtheria antitoxin
  - Snake and spider antivenin
- Diagnostic agents—
  - Iodinated radiocontrast agents
- Venoms—
  - Bees, wasps, spiders, jellyfish
- Hormones—
  - Insulin
  - Hydrocortisone
  - Pituitary extracts
  - Vasopressin

Contd...

Contd...

- Extracts of allergens used for desensitization
- Foods—
  - Eggs
  - Milk and milk products
  - Legumes (peanuts, soybeans, kidney beans, chickpeas)
  - Nuts
  - Shellfish
  - Citrus fruits
- Other drugs—
  - Protamine
  - Parenteral iron
  - Dextrans

Box 2: Conditions in the intensive care unit (ICU) to be distinguished from severe anaphylaxis

- Cardiac problems in the ICU—acute myocardial infarction
- Shock from any other cause—septic shock, hypovolemic shock
- Bronchoconstriction due to aspiration, asthmatic attack, pulmonary edema from other causes
- Pulmonary embolism
- Cerebrovascular accident—causing seizures, hypotension
- Vasovagal syncope

Box 3: Management of anaphylactic shock

- Intubate and administer oxygen at high flow rates. If intubation not possible, emergency tracheostomy or puncture of cricothyroid membrane
- Epinephrine 0.5–1 mL of 1:1,000 solution subcutaneously; this can be repeated every 10 minutes, and is followed by a maintenance infusion of epinephrine
- If no response to subcutaneous epinephrine, or if laryngospasm or cardiovascular collapse present, 5–10 mL of 1:10,000 solution of epinephrine given intravenously (IV)
- If IV access unavailable, 0.5–1 mL of 1:1,000 solution of epinephrine given intramuscularly (IM), or 10 mL of 1:10,000 solution instilled through endotracheal tube
- Administer volume load
- Use antihistaminic, e.g. diphenhydramine 1 mg/kg IV, and repeat 6 hourly
- Relief of bronchospasm by IV aminophylline 250 mg in 20 mL dextrose
- Hydrocortisone 300 mg IV stat, followed by 100 mg IV 6 hourly
- If hypotension persists despite epinephrine, volume load and antihistaminics, start dopamine infusion. If this also does not raise the blood pressure (BP), start epinephrine infusion
- Ventilatory support with high fraction of inspired oxygen (FiO_2) may be required in critically ill patients

CLINICAL FEATURES

Symptoms may occur instantaneously or within a few minutes after an intravenous injection of the offending agent. At times the reaction may develop after 0.5–1 hour of the exposure. Anaphylaxis to oral drugs may take 1–2 hours, but in many patients can be instantaneous.

The major features of anaphylactic shock include hypotension and circulatory collapse due to widespread peripheral vascular dilatation. Severe laryngeal edema and obstruction, angioedema, overwhelming bronchoconstriction and fulminant pulmonary edema may also occur either singly or in combination. Tachycardia, arrhythmias, syncope and seizures at times constitute the predominant clinical features. Diaphoresis, abdominal pain with cramps and diarrhea may occur if death does not ensue following the sinister picture described above. Urticaria is often observed but may be totally absent in patients with fatal anaphylactic shock.

An increased hematocrit is often found due to hemoconcentration resulting from increased vascular permeability.

DIFFERENTIAL DIAGNOSIS (BOX 2)

In a critical care setting, anaphylactic shock in a seriously ill patient may be mistaken for myocardial infarction, hypovolemic or septic shock or pulmonary embolism. Bronchoconstriction due to anaphylaxis may be wrongly imputed to aspiration of gastric contents. A sudden seizure with hypotension may be mistaken for a cerebrovascular accident. A temporal relationship to the administration of intravenous fluids, drugs or blood products should always arouse suspicion of the correct diagnosis.

TREATMENT[3,4] (BOX 3)

The two immediate emergency measures to be instituted in anaphylactic shock are—

1. Intubation to secure the airway before it is blocked by laryngeal edema. Oxygen at high flow rates should be administered. Intubation may be extremely difficult even for an expert. If expert help is unavailable, or intubation fails and there is danger of asphyxia, an emergency airway must be secured (however inadequate this be), by puncturing the cricothyroid membrane by a large bore needle. A tracheostomy should be performed if intubation is impossible, as soon as surgical help is available. An infusion of norepinephrine may also be necessary in patients with persistent hypotension.
2. *Epinephrine which is the first drug to be administered should be promptly given to every patient with anaphylaxis.* We prefer to give it subcutaneously 0.5–1 mL of a 1 in 1,000 solution. This may be repeated every 5–10 minutes,

if necessary. If the patient does not respond to the initial dose, or if laryngospasm or frank cardiovascular collapse is present, 5–10 mL of 1 in 10,000 solution of epinephrine is given intravenously. If intravenous access is not possible, 0.5–1 mL of a 1 in 1,000 solution is given intramuscularly, or 10 mL of a 1 in 10,000 solution of epinephrine may be instilled through the endotracheal tube. A maintenance intravenous infusion of epinephrine may be necessary after the initial bolus dose.

3. Volume load This is the next most important aspect of therapy. In a critical care setting, a venous line is generally already present. We prefer to use crystalloids, though colloids produce quicker volume expansion, for fear of inducing further allergic reactions to colloidal solutions. Short, wide peripheral catheters permit quicker fluid infusions than long, thin central venous lines. Again, collapse of large veins due to circulatory shock increases the risk of iatrogenic complications associated with the insertion of central lines. An iatrogenic pneumothorax, for example, in such a patient would compound difficulties in management.

After the above management protocol has been instituted, one can use an antihistaminic like diphenhydramine 1 mg/kg intravenously, and repeat the dose 6 hourly, if necessary. Aminophylline 250 mg intravenously in 20 mL dextrose helps reduce the bronchospasm. Hydrocortisone 300 mg intravenously, followed by 100 mg 6 hourly may prevent the late manifestations of anaphylaxis. Steroids have little or no role in the immediate alleviation of anaphylactic shock.

If hypotension persists after the use of epinephrine, volume load and antihistaminics, a dopamine infusion starting with 5 μg/kg per minute and titrated if so required to 10–20 μg/kg per minute is infused to increase the blood pressure (BP). If dopamine proves ineffective, then an infusion of epinephrine in a concentration of 3–4 μg per minute is started and slowly increased till a rise in BP is observed. Patients receiving beta-blockers at the time of acute anaphylaxis may fail to respond adequately to epinephrine. Intravenous atropine and glucagon are useful aids to reverse circulatory shock in such patients. Critically ill patients may need both cardiovascular support and ventilatory support with a high fraction of inspired oxygen (FiO_2) till such time as recovery slowly ensues.

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SECTION

7

Cardiovascular Problems Requiring Critical Care

- Acute Coronary Syndromes
- Unstable Angina
- Acute Myocardial Infarction
- Acute Left Ventricular Failure with Pulmonary Edema
- Tachyarrhythmias in the Intensive Care Unit
- Bradyrhythms and Heart Block in the ICU
- Antiarrhythmic Drugs Used in the ICU
- Hypertensive Emergencies and Aortic Dissection in the ICU
- Pulmonary Embolism

CHAPTER 19

Acute Coronary Syndromes

GENERAL CONSIDERATIONS

Acute coronary syndromes are due to an acute disturbance in coronary artery circulation resulting in myocardial ischemia, which if severe or prolonged, could progress to myocardial infarction (MI). The syndrome includes the classical triad of unstable angina, ST segment elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI). The ST elevation myocardial infarction may also have a pathological Q-wave in the anterior chest leads in an anterior myocardial infarction, and in the inferior leads in an inferior myocardial infarction. The NSTEMI may occasionally also have pathological Q-waves over the area of the infarction. These are not separate entities but form a related continuum of the same disease process. Even so, each of these three acute coronary syndromes has a differing prognosis and specific strategies in management.

Critical care, therefore, demands that patients presenting with ischemic cardiac pain be placed into one of these three syndromes. This can be achieved by integrating the history and clinical findings with the evolution in time of the twelve lead electrocardiograms and the quantification over time of the biological markers of myocardial cell necrosis. Since acute coronary syndromes form a dynamic continuum, patients diagnosed to start with as unstable angina, during observation and investigation over time, may ultimately develop into a STEMI or NSTEMI. The dividing line between unstable angina and myocardial infarction may at times be tenuous. Microinfarction detected by a slight rise in the newer sensitive biological cardiac markers may well be an additional event between unstable angina and classical MI.[1]

Acute myocardial ischemia, besides producing unstable angina, STEMI and NSTEMI (the classic triad of acute coronary syndromes), can also result in other clinical presentations. These include sudden death, cardiac arrhythmias causing palpitation, presyncope or syncope, acute pulmonary edema due to severe left ventricular failure. These presentations of myocardial ischemia should logically also be included under acute coronary syndromes. They may present without anginal pain and without ECG or biochemical evidence of MI.

PATHOPHYSIOLOGY

Most patients with acute coronary syndromes have significant obstructive atherosclerotic lesions in the coronary arteries. Acute myocardial ischemia can be precipitated either by a sharp reduction in supply of oxygen (e.g. a thrombus obstructing the coronary lumen or vasospasm), or a significant increase in oxygen demand (e.g. an acute rise in the blood pressure or tachycardia). Both a reduction in oxygen supply and an increase in oxygen demand may operate in the same patient.

The major precipitants of the acute coronary syndrome are briefly described below[2]—

- *Rupture or erosion of an atherosclerotic plaque* with a resulting thrombus obstructing the lumen of a coronary artery. This is the most frequent and important pathogenic mechanism. Remarkably enough, the vulnerable plaques (i.e. plaques prone to rupture) are not the tightly stenotic lesions but lesions with usually less than 50% stenosis.[3] These lesions may not be visualized by coronary angiography.

Plaque rupture or erosion is precipitated by biochemical causes. These include liquid lipid content within the plaque, inflammation with erosion of a thin fibrous cap overlying the

plaque and local shear stress forces. A ruptured atherosclerotic plaque exposes the underlying subendocardial matrix to the circulating blood. Initially, this leads to platelet adhesion followed by platelet activation. The latter results in the release of thromboxane A_2, serotonin and other chemotactic agents, which are strong vasoconstrictors. Platelet activation also results in expression and activation of glycoprotein IIB/IIIA receptors on the platelet surface so that it can bind fibrinogen. The final step is platelet aggregation with the formation of a platelet plug over the plaque rupture site. Together with the formation of a platelet plug, there is activation of the coagulation system within the plasma initiated through the release of tissue factor. Activation of factor X to factor Xa leads to the generation of thrombin, which converts fibrinogen to fibrin. Thrombin once formed acts as a powerful stimulus for platelet aggregation; thrombin also activates factor XIII which leads to stabilization of the fibrin clot. The pivotal role of a thrombus partially or completely occluding a coronary artery in the pathogenesis of acute coronary syndromes is supported by substantial evidence.[4]

- *Inflammation and infection* Inflammation may well play an important role in the formation of atherosclerotic lesions and in the erosion or rupture of vulnerable plaques.[5] The role of infectious agents, in particular Chlamydia pneumoniae in causing such inflammation is the subject of current research.[6]
- *Coronary vasoconstriction* Coronary vasoconstriction reduces coronary blood flow and occurs in the following situations—
  - In the presence of coronary atherosclerotic lesions, particularly with plaques.
  - In microcirculatory angina, caused by spasm of intramural vessels.
  - In *Prinzmetal's angina* The latter is associated with severe focal spasm either at the site of a mild to moderate obstructive lesion, or at the site of a non-obstructive plaque, or in patients without coronary atherosclerosis. These patients typically present with severe rest angina with transient ST elevation occurring during episodes of anginal pain.
- *Progressive mechanical obstruction* Progressive luminal narrowing is most frequently observed when restenosis occurs after a coronary angioplasty. However, it can also occur in patients who have no intracoronary procedures performed on them. It is due to rapid proliferation of cells within the stenotic lesion leading to a critical obstruction of the lumen.
- *Increased myocardial oxygen demand* In patients with stable coronary artery disease, a sharp increase in myocardial oxygen demand due to extrinsic factors may precipitate the acute coronary syndrome, particularly unstable angina. Increased myocardial oxygen demand occurs in—
  - Sudden increase in blood pressure; in increasing aortic stenosis.
  - Tachycardia due to fever, anemia, thyrotoxicosis, supraventricular tachycardia, atrial fibrillation with a fast ventricular rate, other hyperdynamic circulatory states.

  The acute coronary syndrome could also be precipitated or worsened by—
  - Impaired oxygen delivery as in patients with a low output syndrome, anemia, hypoxia from any cause, hyperviscosity states.
  - Metabolic derangements, in particular hypoglycemia.

The clinical determinants of the acute coronary syndromes are related to the severity and duration of myocardial ischemia.

Unstable angina is generally induced by a temporary, non-occluding thrombus within the coronary artery lumen.[7] Thrombus formation is a dynamic process; a thrombus after being formed may in time be fibrinolyzed. Temporary and repeated accretions of fresh thrombi over the site of plaque rupture may critically narrow the lumen to produce rest angina. Partial spontaneous resolution of the thrombus within 10–20 minutes would provide relief and this generally occurs in unstable angina.

In a NSTEMI, the thrombus is larger and generally does not completely occlude the lumen. It may cause significant obstruction for 20–30 minutes before being partially, or at times completely, resolved. The degree of myocardial ischemia is significantly great to cause myocardial necrosis with liberation of cardiac enzymes.

In a STEMI, there is a thrombus that completely occludes a coronary vessel in over 95% of patients. This can lead to fairly extensive necrosis (often associated with a Q-wave), surrounded by an area of injury, which is in turn surrounded by an area of ischemia.

Whether a partially or a completely obstructing thrombus in a coronary artery results in unstable angina, a ST elevation infarct or a non-ST elevation infarct, will to an extent be also influenced by the presence or absence of coronary collaterals, by the degree of coronary vasoconstriction and by associated increase in myocardial oxygen demand.

It is to be noted that the earlier classification of MI into subendocardial and transmural has been given up, as these descriptions are clinically inaccurate when correlated with autopsy findings.

The subsequent sections now deal with the diagnosis and management of unstable angina and MI.

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CHAPTER 20

Unstable Angina

INTRODUCTION

Acute total occlusion of a coronary artery results in a ST elevation myocardial infarction (STEMI), whereas severe but not total occlusion results in unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI). UA or NSTEMI is a condition now also referred to as non-ST elevation acute coronary syndrome (NSTE-ACS). The incidence of NSTE-ACS both in absolute terms and also relative to STEMI is increasing. In India, this is largely due to the high and increasing incidence of diabetes in the population; diabetes being an important risk factor for UA or NSTEMI. In the West and the USA, both diabetes and an increasing number of older people are equally responsible for this rise.[1]

Unstable angina or non-ST elevation myocardial infarction signifies a seriously prejudiced circulation in one or more coronary arteries and carries a risk of serious cardiac arrhythmias, cardiac failure and sudden death. The problem therefore is of immense concern and of great importance to the critical care physician.

Though figures for our country as a whole are not available, in the Western world and in the USA, among patients with the ACS, women present more often with UA, representing 35–45% of patients with this condition compared with 25–30% of patients with NSTEMI and only 20% of patients with STEMI.[2] Approximately, 80% of patients with UA or NSTEMI have a history of coronary artery disease before the acute event.

The diagnosis of UA depends on the presence of one or more of the following—

- New-onset angina, i.e. angina occurring for the first time within a one-month period, and brought on by minimal exertion.
- Increasing severity of a previously stable angina. This may take the form of more protracted anginal pain, or pain with more extensive radiation, or more frequent angina (more than three times a day), or angina brought on by less effort or by other precipitating factors which previously had not produced any discomfort. Angina, which is incompletely relieved or unrelieved by nitroglycerin, also denotes a worsening pattern and constitutes UA. The increase in frequency and severity of angina is superimposed on a pattern of a relatively stable exertion-related angina.
- Rest angina denotes anginal episodes at rest. In the acute or emergent form, many such anginal episodes may occur over 24 hours. At times, angina at rest may occur more frequently at night. In the less emergent (yet dangerous) situations, rest angina may occur at infrequent intervals after lapses of two or more days.

Approximately two-thirds of patients with UA have elevated cardiac enzymes—troponin I or T and creatinine kinase isoenzyme (CPK-MB) in the blood. These patients are diagnosed to have NSTEMI. As measurements of troponin levels in the blood become increasingly sensitive, a greater number of patients with NSTE-ACS will demonstrate some release of troponin; these should be considered as NSTEMI. As a corollary, a diagnosis of NSTEMI can only be made if troponin levels are increased against a background of clinical features of myocardial ischemia.

Braunwald[3] has proposed a clinical classification of UA or NSTEMI taking into consideration three degrees of clinical severity, three clinical circumstances, the response to medical therapy and the presence or absence of electrocardiographic changes. The increasing degree of clinical severity is classed as follows[3]—

- Class I—severe or frequent new onset angina (<2 months).
- Class II—rest angina in the past month, but not during previous 48 hours.
- Class III—anginal attacks at rest within prior 48 hours.

The three clinical circumstances considered by Braunwald are as follows[3]—

1. Patients with secondary angina (Class I); there is a secondary cause that exacerbates angina (e.g. anemia, fever, hypoxemia, tachyarrhythmia, thyrotoxicosis, hypoglycemia).
2. Patients in whom no precipitating cause can be found (Class II).
3. Patients with postinfarction angina (within 2 weeks of a myocardial infarct).

Braunwald[3] also considered symptom severity and clinical circumstances of a given patient in relation to treatment—whether the patient was not on treatment prior to unstable angina, on treatment for previous stable angina, and finally whether unstable angina persisted in spite of maximal treatment. Braunwald's classification has been shown to correlate with clinical outcomes. Patients with severe angina (Class III), poor response to full medical treatment, ST-T changes on the ECG, and those with postinfarction angina have poorer outcomes.[4] A higher clinical grading was predictive of plaques with thrombus at angiography.[4]

The diagnosis of UA rests chiefly on a good clinical history. The basic characteristics of the pain are similar to those observed in stable angina. The pain is substernal and often precordial, and is described as heaviness, constriction, and at times, as just severe pain. It is often interpreted as a feeling of choking in the chest or throat. In UA, the duration of pain may be as long as 15 minutes and may extend to even 30 minutes. The typical sites of radiation include the left shoulder, arm, forearm, hand, right shoulder and upper arm, shoulders and arms, the jaw, the neck, the back and the upper abdomen. On occasion, the pain may not be felt in the chest at all, but may only be experienced at one or more sites of radiation mentioned above.

The diagnosis of UA in a patient with a past history of myocardial infarction (MI), or a typical history of angina on effort, generally presents no difficulty. New onset angina characterized by frequent chest pain at rest may require careful evaluation of the history and a close follow-up, to help distinguish it from nonanginal or noncardiac pain. There are some important negative points that help in the diagnosis of ischemic heart pain—

- Pain localized to the apex is almost always nonanginal.
- Jabbing or pricking pain is also generally nonanginal in etiology.
- Pain which worsens on local pressure or pain which is clearly aggravated by movement is also definitely nonanginal.

Physical findings in UA are more often than not negative. During an attack of pain, one may hear a third heart sound at the apex, a reversed split of the second sound at the base, and a mid to late mitral systolic murmur of papillary muscle dysfunction. Rarely, frequent extrasystoles or even supraventricular or ventricular arrhythmias occur after the onset of pain, and may disappear after the pain subsides.

ECG Transient ST elevation or depression, or T-wave inversion may occur during the pain. However, absence of ECG changes even during periods of severe cardiac pain in no way rules out a diagnosis of UA. Continuous ECG monitoring may at times reveal ST depression characteristic of myocardial ischemia or may detect transient arrhythmias. Not uncommonly ST-T changes are of a nonspecific nature. Transient (<20 minutes) ST elevation, which occurs in approximately 10% of patients with UA or NSTEMI, prognosticates a higher risk of a cardiac event. T-wave changes are sensitive but not specific for myocardial ischemia, unless T-wave inversions are deep and symmetrical.

In patients with a past history of ischemic heart disease (IHD), or when previous investigations clearly denote IHD, the diagnosis of UA can be confidently made on a history alone, even in the absence of ECG changes during episodes of pain. It is only in the group of patients without a history of previous stable angina or previous IHD, that the diagnosis of UA without any ECG changes becomes difficult or inaccurate.

Serum Cardiac Enzyme Levels Among patients presenting with symptoms of UA or NSTEMI a rise in the troponin T or I or the CPK-MB identify those suffering from NSTEMI, which has a worse prognosis. Troponin levels are more sensitive than CPK-MB levels.

The Gusto II Trial[5] showed that elevated levels of troponin T are associated with a higher risk and a higher 30-day mortality. Higher levels of troponin T correlated more strongly with 30-day survival than either ECG changes or changes in CPK-MB levels. Low levels of troponin T were noted to be associated with a low rate of cardiac events. Low troponin levels do not always signify a good prognosis, for catastrophes can still occur.

Specific Unstable Angina Syndromes

- *Unstable angina after angioplasty* Unstable angina after angioplasty is related to restenosis and occurs in over 30% of patients. It may present as angina at rest.
- *Unstable angina after bypass surgery* If this occurs within 6 months after surgery it may signify a single active lesion. Later it often signifies obstruction to venous grafts.
- *Prinzmetal's angina* is a vasospastic variant of UA (see Acute Coronary Syndromes). The pain in this variant typically occurs at night or in the early hours of the morning. It is characterized by transient ST elevation during pain and is relieved by nitroglycerin and by calcium channel blockers.

Risk Stratification

Risk stratification in UA or NSTEMI is important as it helps to determine which patients are at greater risk for impending or near-future cardiac events like sudden cardiac death,

arrhythmias, left ventricular (LV) failure. In essence, it helps to assess possible outcomes in patients presenting with UA or NSTEMI. Risk stratification also helps the critical care physician to decide on the appropriate strategies for management.

High-Risk Subgroup

Clinical Assessment

Advanced age greater than 70 years is associated with a poorer outcome, as is the presence of diabetes, congestive heart failure, or the presence of extracardiac vascular disease such as peripheral vascular or cerebrovascular disease.

Braunwald's clinical classification of UA or NSTEMI has been found to be useful in several studies. High-risk patients include those with ongoing protracted angina, recurrent rest angina, angina unresponsive to medical therapy and postinfarction angina.

Risk Assessment by ECG

The presence of left bundle branch block is believed to be an independent predictor of death in MI. Also the greater the degree of ST depression in the ECG, the greater the risk for cardiac events.[6]

Risk Assessment by Estimation of Cardiac Markers-Troponins and CPK-MB Levels

Patients with NSTEMI identified by a rise in troponins or CPK-MB levels have a worse long-term prognosis compared to those with UA.[7]

Beyond just a positive report, the higher the level of subsequent troponins, the higher the risk of subsequent death in these patients.[8]

Assessment of Other Inflammatory Markers

A significant rise in the CRP indicates an increased risk of death, MI and the urgent need for revascularization. Among patients with negative troponin I, CRP can distinguish between high-risk and low-risk groups. When both CRP and troponins are used, mortality ranges from 0.4% for patients with both markers negative to 4.7% if either CRP or troponin is positive to 9.1%, if both are positive.[9]

7

MANAGEMENT OF UNSTABLE ANGINA AND NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

General Principles

Unstable angina and non-ST segment elevation myocardial infarction spell danger and the patient must be admitted in the intensive care unit (ICU). The ECG should be continuously monitored, an intravenous (IV) line secured and serial enzyme estimates of CPK-MB and troponins should be done.

There are three approaches to management. The first is a conservative approach with medical management. The second is an early invasive strategy involving percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The third approach is initial conservative management, which graduates to coronary angiography and invasive intervention in patients who develop worsening myocardial ischemia or develop LV dysfunction or hemodynamic instability.

The most suitable approach to the management of ACS patients who present without ST elevation is dependent on risk stratification. Risk stratification begins on entry into the ICU but continues during hospital stay. It is important to determine as to which patients with UA are likely to progress to MI or suffer death as also which patients with NSTEMI are more likely to worsen, suffer complications or die. Risk stratification with regard to clinical assessment, ECG changes and elevated cardiac enzymes has already been discussed earlier in this chapter. As a general principle, the higher the risk the more the need for an invasive strategy of coronary angiography. Conservative management could be the first or preferred approach in those stratified to be low or medium risk.

Emergency Management

Bed rest is important particularly for patients with protracted angina, recurrent angina or repeated rest angina. The patient is given 300 mg aspirin to be chewed and swallowed as also 300–600 mg clopidogrel to be promptly swallowed. Sorbitrate 5 mg sublingually can be repeated after 5 minutes with close monitoring of the blood pressure and clinical effects.

If pain is unrelieved or even otherwise with a history of protracted cardiac pain, IV nitroglycerin is started. Severe pain may require the initial use of IV morphine (2–4 mg) or IV buprenorphine (0.3 mg). It is crucial to relieve pain; pain induces an increased catecholamine state, which increases anxiety, heart rate, blood pressure and cardiac contractility, thereby increasing myocardial oxygen demand and myocardial ischemia. In the presence of hyperadrenergic states, the judicious use of beta-blockers is of great help.

A constant watch on clinical findings and on the ECG recording is imperative to promptly detect complications, in particular arrhythmias, LV dysfunction and failure, hypotension and early signs of cardiogenic shock.

A quick but careful search for possible factors aggravating or precipitating angina should be made and if possible these should be corrected. Increased myocardial oxygen demand with resulting angina can occur with fever, tachycardia, thyrotoxicosis, tachyarrhythmias, bradyarrhythmias or hypoglycemia. Hypovolemia due to fluid loss in vomiting and diarrhea can also precipitate UA or NSTEMI. In patients with asthma or chronic lung problems, exacerbation of their pulmonary disease can produce hypoxemia, which in turn worsens angina. Recent blood loss as from a gastro-intestinal bleed or anemia from any cause can also precipitate

Box 1: Management of unstable angina

- *General Measures*—
  - Critical care monitoring
  - Serial estimations of troponin T, troponin I, CPK-MB to exclude acute MI
  - Sublingual nitroglycerin to relieve myocardial ischemia
  - Diazepam for relief of anxiety
  - Morphine 2–4 mg IV, if pain severe
- *Nitrates*—
  - Nitroglycerin drip at 10 µg/min, and gradually increased till angina controlled. Systolic BP should not fall less than 100 mm Hg
  - Later oral isosorbide dinitrate 10 mg 6 hourly, or sublingual isosorbide dinitrate or nitroglycerin patch
- *Beta-blockers*—
  - For ongoing severe pain—metoprolol 5 mg IV repeated at 5-minute intervals to a maximum total dose of 15 mg—watch heart rate, BP; then oral metoprolol or propranolol titrated to maintain heart rate between 55–60/min
- *Calcium antagonists*—
  - Use only if ischemia persists in spite of nitrates and β-blockers, Diltiazem 30–60 mg 8 hourly or verapamil 40 mg 8 hourly
- *Anticoagulants, antiplatelet drugs, Glycoprotein (Gp) IIb-IIIa receptor inhibitors*—
  - Either unfractionated heparin (IV 5,000 units bolus, followed by 500–1000 units/hour) for 3–7 days or low molecular weight heparin (enoxaparin 1 mg/kg 12 hourly) for 3–7 days + aspirin 300 mg + clopidogrel 75 mg daily. Eptifibatide (180 µg/kg IV, followed by infusion of 2 µg/kg/min for 96 hours) or tirofiban (loading dose 0.4 mg/kg/min for 30 minutes, followed by 0.1 mg/kg/min for 96 hours, together with unfractionated heparin could be used in refractory or high-risk unstable angina. Risk of bleeding with this therapy
- *Treat factors precipitating or aggravating unstable angina*
- Coronary angiography–indicated if pain is unrelieved or marginally relieved with the above treatment, or if anginal episodes worsen. Early coronary angiography in high-risk patients with UA/NSTEMI

Abbreviations: CPK-MB, creatinine kinase isoenzyme in blood; MI, Myocardial infarction; IV, intravenous; BP, blood pressure.

UA or NSTEMI. A careful assessment of the associated problems outlined above may help in overall management and result in a quick stabilization of the angina (Box 1). Acute mental stress from whatever cause should be promptly recognized and benzodiazepams given to relieve anxiety. Box 2 lists the important aggravating or precipitating factors for UA.

Nitrates

Nitrates act as coronary vasodilators and also act by reducing the preload and therefore the work performed by the heart. They can be given sublingually, orally (5–10 mg isosorbide dinitrate 6 hourly) or intravenously. Intravenous nitroglycerin is preferred in patients with recurrent or protracted or rest angina, as the onset of action is immediate and the drug can be titrated with a fair degree of precision. The dose and method of administration and untoward effects are detailed in the chapter on STEMI. Nitrates should be avoided if there is history of use of sildenefil in the past 24 hours as otherwise there could occur a disastrous and at times fatal hypotension. Tachyphylaxis is often observed with nitroglycerin in that its antianginal effect is reduced despite constant drug infusion. The infusion rate should be increased slightly by about 10% every 24 hours to maintain efficacy. The patient is generally weaned off nitroglycerin 2–3 days after angina ceases or has markedly eased and then started on oral isosorbide dinitrate. A topical 1–2" nitroglycerin patch or paste can be applied to the skin as an alternative.

Box 2: Important aggravating or precipitating factors for unstable angina

- Fever
- Tachycardia
- Thyrotoxicosis
- Tachyarrhythmias
- Bradyrhythms
- Hypoglycemia
- Hypovolemia due to fluid loss in vomiting and diarrhea
- Exacerbation of pulmonary diseases like COPD, asthma
- Recent blood loss (as from a GI bleed) or anemia from any cause
- Acute mental stress

Abbreviations: GI, gastrointestinal; COPD, chronic obstructive pulmonary disease.

Beta-blockers

Beta-blockers in combination with nitrates have been shown to reduce symptoms of myocardial ischemia.[10-12]

They are particularly useful in those who have a tachycardia, provided the latter is not due to LV failure or hypovolemia. Severe UA or NSTEMI are at times associated with a hyperadrenergic state characterized by marked tachycardia, hypertension, pallor, sweating. Beta-blockers effectively counter these hyperadrenergic effects. It is to be noted that a sudden withdrawal of beta-blockers in patients who are on this drug prior to the onset of UA or NSTEMI can cause marked tachycardia and at times hypertension. Restarting beta-blockers in these patients solves the problem. The mode of administration, sideeffects, indications and contraindications have been dealt with in the chapter on STEMI.

Calcium Channel Antagonists

Calcium channel antagonists are currently recommended only in patients who have persistent ischemia in spite of the use of nitrates and beta-blockers or in patients in whom beta-blockade is contraindicated.

Diltiazem or verapamil are calcium channel blockers which slow the heart rate. They are given in a dose of 30–90 mg four times a day, both in UA and in NSTEMI.[13] Amlodipine or felodipine can also be used safely but nifedepine has been shown to increase adverse events when not co-administered with a beta-blocker. Diltiazem is best avoided in patients with left ventricular dysfunction or congestive cardiac failure because of its negative inotropic effect.

Unstable angina or NSTEMI also needs the prompt administration of antiplatelet therapy and anticoagulants. Finally, the intensivist and the cardiologist should take a decision on the need and the timing for interventional management.

Antiplatelet Therapy

Aspirin

The use of aspirin has already been commented upon. The drug acetylates platelet co-oxygenase-1 (COX-1) and thereby blocks the synthesis and release of thromboxane A_2, a platelet activator. Aspirin thereby decreases overall platelet aggregation and prevents arterial thrombi formation. Several studies have shown the beneficial effects of aspirin in UA or NSTEMI. The drug reduces adverse clinical events in the early course of treatment and also prevents recurrence of ischemic episodes in secondary prevention.

Aspirin reduces the risk of death in MI in 50% of patients with UA or NSTEMI. This was observed both on the Veterans Administration (VA) Cooperative Study Group[14] and the Canadian Multicenter Trial.[15]

Ticagrelor

Ticagrelor, the first reversibly binding, direct-acting oral P2Y12 receptor antagonist has been FDA-approved as an oral antiplatelet agent for the prevention of thrombotic events, in patients with acute coronary syndromes (unstable angina, NSTEMI and STEMI). Ticagrelor and its major metabolite reversibly interact with the platelet P2Y12 ADP-receptor to prevent signal transduction and platelet activation.

The recommended dosage is 180 mg—loading dose followed by 90 mg twice daily as the maintenance dose.

ADP Antagonists

Thienopyridines

These agents include clopidogrel, prasugrel and ticlopidine.

Clopidogrel Patients admitted with a diagnosis of UA or NSTEMI should be given clopidogrel in addition to aspirin. The initial dose of clopidogrel is 300–600 mg followed by a maintenance dose of 75 mg. The antiplatelet effect of clopidogrel is observed within 4 hours if 300–600 mg is given. On the other hand, a daily dose of 75 mg clopidogrel would need 4–7 days for antiplatelet effect. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) Trial[16] observed that the use of this combination resulted in a decrease in cardiovascular death, MI or stroke not only in patients who undergo PCI but also in patients who receive medical treatment.

Prasugrel It is also a reasonable choice of an antiplatelet agent in place of clopidogrel in patients with ACS. There is however a greater risk of bleeding and it should not be used in patients with history of stroke or transient ischemic attack (TIA) and avoided in patients older than 75 years.

Prasugrel is administered as a 60 mg loading dose followed by 10 mg/day maintenance dose. The duration of clopidogrel therapy depends on whether the patient has received a stent. It is at least 4 weeks (preferably 3 months) if it is a bare metal stent and tentatively at least 12 months if it is a drug eluted stent.[17,18] More data is required to give a definite recommendation on the duration of clopidogrel therapy in patients with drug eluted stents.

Anticoagulant Therapy[18]

Unfractionated heparin given IV has been the mainstay of the treatment of UA or NSTEMI for several years. Therapy with unfractionated heparin plus aspirin has been shown to lead to a 33% reduction in death or MI compared to aspirin alone. Current guidelines advise a weight adjusted dose of 60 units/kg bolus, followed by 12 units/kg per hour with 6 hourly monitoring of activated partial thromboplastin time (APTT) which should be kept at 2–2½ times the control. The dose may need titration to maintain the required APTT time. Adverse effects include bleeding particularly if the APTT is unduly high and heparin induced thrombocytopenia.

Low molecular weight heparin (LMWH) is now often preferred to unfractionated heparin in the treatment of NSTEMI, the dose being the same as that recommended for STEMI. LMWH has the following advantages—

- A more predictable anticoagulant response, so that estimation of partial thromboplastin time (PTT) is not necessary.
- A lower incidence of heparin induced thrombocytopenia.
- Easily administered and therefore suitable for administration over a longer period of time.
- The LMWH enoxaparin reduced the combined endpoints of death, MI or recurrent ischemia at both 14 days and 30 days when compared to unfractionated heparin. It is given by injection subcutaneously in a dose of 1 mg/kg every 12 hours. Patients older than 75 years or who have renal dysfunction need a reduced dose of 0.5–0.75 mg/kg every 12 hours.

Direct Thrombin Inhibitors

Bivalirudin is the only direct thrombin inhibitor indicated for the use of acute coronary syndrome.[18] Its use when combined with heparin even in combination with glycoprotein IIb/IIIa inhibitors does not confer any added advantage. Most units in this country are unfamiliar with its use.

Glycoprotein IIb/IIIa Receptor Antagonists

Glycoprotein IIb/IIIa receptor antagonists block the fibrinogen mediated cross-linkage of platelets. The three agents available in this class are (1) Abciximab, a monoclonal agent approved only in patients undergoing PCI, (2) Eptifibatide and (3) Tirofiban (small molecule inhibitors).[18] Each drug when administered is given as a IV bolus followed by a continuous infusion. Their blocking activity and the associated risk of bleeding subside once the infusion is stopped.

The benefits of glycoprotein IIb/IIIa receptor antagonists in patients with UA or NSTEMI has been reported to be a significant 11% relative reduction in death or MI at 30 days.[19] This benefit is greater in high-risk patients such as those with marked ST segment changes and high troponin levels as also in diabetics. These subgroups have more thrombosis at coronary angiography with a greater risk of microembolization.

For patients with UA or NSTEMI undergoing an initial invasive approach, the current recommendations are to administer either a glycoprotein IIb/IIIa receptor antagonists or clopidogrel in additon to aspirin and heparin. However, if the patient is considered high-risk, both a Glycoprotein IIb/IIIa receptor antagonists plus clopidogrel can be given in addition to heparin.

It is to be noted that the risk of major bleeding is significantly higher for patients treated with glycoprotein IIb/IIIa receptor antagonists, occurring 2.4% compared to 1.4% for placebo. The risk of thrombocytopenia (<50,000/mm^3) is greater in those treated with glycoprotein IIb/IIIa receptor antagonists than with heparin alone.

Interventional Management

When should interventional management be undertaken? Coronary angiography serves three purposes: (1) it helps in risk stratification by demonstrating the extent and severity of coronary artery disease; (2) it is a prelude to possible revascularization either through angioplasty or CABG surgery, and (3) it can confirm or refute the presence of epicardial coronary artery obstruction when the diagnosis of UA or NSTEMI is in doubt.

Indications for Coronary Angiography and Invasive Interventional Strategies in UA or NSTEMI

Several randomized recent trials and meta-analysis have advocated an early invasive strategy in patients who have the following features—

- ST segment changes or positive troponins on admission or if these evolve over the subsequent 24 hours.
- Recurrent angina, protracted angina, poor relief on medical therapy, persistent angina on rest.
- Evidence of left heart or congestive heart failure.
- UA or NSTEMI within 6 months of a prior PCI and in whom a blocked stent may be the cause.
- UA or NSTEMI in a patient with prior CABG.
- Hemodynamic instability.
- Ventricular arrhythmias.

The risk of an invasive strategy increases in the presence of hemodynamic instability but the risk of continuing with conservative medical management is perhaps greater.

Two studies which advocate a strategy of early invasive intervention are given below.

The Intracoronary Stenting with Antithrombotic Regimen Cooling Off (ISAR-Cool) trial showed a benefit of immediate invasive strategy with an average time of only 2 hours from randomization to catheterization, compared to delayed strategy in which the average time to catheterizations was 4 days.[20]

The Timing of Intervention in Patients with Acute Coronary Syndromes (TIMACS) trial[21] again showed a trend for reduction of the primary end-point (death, MI, stroke) in patients submitted to an early invasive strategy. There was an even more significant reduction in the primary end-point in patients with a high GRACE risk score. There was also a significant 28% reduction of the secondary endpoint of death, MI and refractory ischemia in the group. Both these trials lend support to an early interventional strategy particularly in high-risk patients.

Notwithstanding the evidence gathered from studies mentioned above, a wise physician should always place clinical judgment ahead of statistical evidence gleaned from a study of large groups of people. Besides patient factors, the physician should consider the expertise and experience of the interventional cardiologist, the facilities available if urgent need for CABG arises, the cost to the patient, the degree of improvement in the quality of life likely to accrue through the procedure. High-risk patients particularly those who are hypotensive, in pump failure or have recurrent arrhythmias need aortic balloon support before and during coronary angiography and angioplasty. An intra-aortic balloon counter pulsation device can cause lower limb ischemia in 10% of cases. A close watch over pulsations in the lower limb should be maintained.

Coronary angiography in UA not responding to conventional medical therapy helps to identify several subgroups (Box 3).[22]

- Patients with a left main stenosis who require emergency bypass surgery.
- Patients with severe triple or multivessel disease who are advised bypass surgery within 7–10 days on a semi-urgent basis.
- Patients having multivessel disease with LV dysfunction, or diabetes with multivessel disease, who also will require bypass surgery to help prolong their life-span.
- Patients with single or two vessel disease with an identifiable culprit lesion. These patients are suitable for angioplasty. Current angioplasty success rates are over 95%.[23]

Box 3: Subgroups (with management) identified by coronary angiography in patients with unstable angina

- Patients with left main coronary artery disease—urgent bypass surgery indicated
- Patients with severe triple or multivessel disease (including proximal LAD)—bypass surgery advised on semi-urgent basis (7–10 days)
- Patients with multivessel disease and LV dysfunction; patients with multivessel disease and diabetes—bypass surgery required to improve long-term survival
- Patients with single or double vessel disease with identifiable culprit lesion in form of proximal discrete stenosis—angioplasty with stenting is procedure of choice
- Patients with diffuse distal coronary artery disease—medical therapy indicated as surgery gives poor results
- Small minority of patients (5%) with no demonstrable organic coronary artery disease—medical management indicated

Abbreviations: LAD, left anterior descending artery; LV, left ventricular.

Yet, there is an increased rate of acute complications in the form of abrupt closure of the vessel or MI, following angioplasty in patients with UA, or in those with a visible occluding thrombus, when compared to patients with stable angina or in those in whom a thrombus is not visible. The use of coronary stents has, however, reduced the incidence of emergency bypass surgery, and the increasing use of glycoprotein IIb/IIIa inhibitors has reduced the incidence of death and MI.

- Patients with diffuse distal coronary artery disease for whom only medical therapy is advocated, as surgery shows poor results.
- A small minority of patients (in our experience 5%) with no significant organic coronary artery disease, who should continue with medical treatment.

After a successful angioplasty with stenting of a culprit vessel, the patient is monitored in the ICU. Sudden occlusion of the vessel on which angioplasty is done (blockage of the stent) results in cardiac pain, and ECG changes of impending infarction. This constitutes an emergency, which is tackled by either attempting to reopen the vessel by performing a fresh angioplasty, or by doing an emergency coronary artery bypass surgery. A standby surgical team should always be present when an angioplasty is done.

Patients with UA who respond to medical treatment will subsequently require a work-up to determine the nature and extent of their coronary artery disease so that elective treatment can be planned. This is done preferably 7–10 days after symptoms related to UA or NSTEMI have been well controlled, though many units would prefer to do coronary angiography earlier.

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CHAPTER 21

Acute Myocardial Infarction

GENERAL CONSIDERATIONS

Acute myocardial infarction (AMI) signifies ischemic necrosis or death of a portion of the myocardium. Atherosclerotic narrowing of the coronary vessels is the basic underlying pathology in most patients, and an occluding thrombus is usually present in a major coronary artery or its branch. Myocardial infarction (MI) still carries an overall mortality between 10–30%. Prompt diagnosis and early transfer to a critical care unit, whenever possible, are essential if mortality is to be reduced. The importance of quick diagnosis and early transfer to a well-equipped intensive care unit (ICU) is related to two factors—

1. Fifty percent of deaths in AMI occur within the first 2 hours, and 80% within the first 24 hours. Early deaths occurring during this period are invariably due to primary ventricular fibrillation which can be promptly treated with good results in an ICU setting.
2. The present day management of AMI involves not only the relief of pain and other supportive treatment, but an active interventional approach directed toward restoring blood flow to the ischemic myocardium. This interventional approach is through the use of thrombolytic agents with a view to dissolving a thrombus occluding a coronary artery, and/or in selected instances the use of angioplasty to physically open and stent an occluded vessel. The earlier, this is done after the onset of MI, the better the results.

In the past, MI was considered to be either a Q-wave (transmural) infarction or a non-Q (nontransmural) infarction. This terminology was replaced by MI with ST-segment elevation (ST-elevation MI (STEMI) or MI without ST-segment elevation (non-STEMI or NSTEMI). In STEMI, clinical features of myocardial ischemia coupled with raised ST-segment in the electrocardiograph (ECG) determined treatment. In NSTEMI, clinical features of myocardial ischemia are not associated with diagnostic elevated ST-segments on the ECG. A rise in serum markers over time is necessary to indicate a NSTEMI. This terminology still prevails. However, MI has been more recently further defined and categorized according to the many different clinical situations in which it can occur.

In 2007, The European Society of Cardiology and the American College of Cardiology along with the World Heart Federation and American Heart Association published the Universal Definition of MI. This definition classifies infarction based on different clinical situations in which MI occurs.[1]

The term MI signifies evidence of myocardial necrosis in the presence of clinical features consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis. The different types of AMI are—

Type 1 Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion. The type 1 of AMI demonstrates a typical rise and/or fall of cardiac biomarkers (preferably troponin), with at least one value above the 99th percentile of the upper reference limit (URL), together with evidence of myocardial ischemia manifested by at least one of the following—

- Symptoms of ischemia.
- Electrocardiographic changes indicative of new ischemia [new ST-segment and/or T-wave changes or a new left bundle branch block (LBBB)].
- Development of pathologic Q-waves on the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Type 2 Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply (e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, severe hypertension or significant hypotension).

Type 3 Sudden, unexpected cardiac death involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood.

Type 4 Myocardial infarction associated with percutaneous coronary interventions (PCI), with or without intracoronary stent. For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 3 × 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.

Type 5 Myocardial infarction associated with coronary artery bypass graft (CABG). For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 5 × 99th percentile URL plus either new pathologic Q-waves, or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI. Also, pathological findings of an AMI define the type 5 AMI.

A patient with an AMI may be admitted to the ICU from the community. On the other hand, a patient who is already being treated for a critical ailment may develop AMI as an added complication. Septic shock or hypovolemic shock for example, could cause either a STEMI or a NSTEMI due to the added physiological stress on the heart. This is even more likely to occur in older patients with coronary artery disease which may have been clinically silent prior to the critical illness. Also, such a patient could conceivably have no clinical evidence of myocardial ischemia if he were obtunded, sedated and/or on ventilator support.

It is not the purpose of this chapter to extensively detail the pathophysiology, clinical features and diagnosis of AMI. Only the basic features of diagnosis are touched upon so that mistakes are perhaps less frequent and management is not unnecessarily delayed.

DIAGNOSIS

Notwithstanding the current subclassification of MI, the diagnosis of AMI in a patient admitted to the Emergency Department or ICU is based on a positive history of cardiac pain, ECG changes, and elevated cardiac enzymes. A diagnosis should be made if any two of these three factors are present. In those patients who show no early serial ECG changes, a 4 hourly serial estimation of the cardiac enzyme in particular the troponin T, troponin I, creatine kinase (CK) and the CK-myoglobin (CK-MB) fraction should be monitored. A rise in the troponin levels, even if a little delayed, confirms the diagnosis. If, however, quick interventional therapy is to be instituted to salvage myocardium, a diagnosis has to be made on the history (and clinical findings), and on the ECG changes, as the rise in cardiac enzymes may take time to detect.

Cardiac pain is the most important clinical feature of AMI. In some, the pain is agonizingly severe, while in others it may be so mild as to be totally ignored by the patient and overlooked by the doctor. It is not necessarily the severity of pain, but the site and radiation of pain, as well as its character, which are diagnostic. The character of the pain is as in angina, felt substernally and over the precordium with radiation to the shoulder, arms, neck or jaw. Patients with AMI may present with pain in the right chest or one single site at which ischemic cardiac pain is known to radiate. At times patients with inferior myocardial infarct may complain of severe headache as the main site of pain. Whereas pain in angina lasts less than 15 minutes, patients with AMI generally experience protracted pain over 30 minutes. Pain is often accompanied by associated features, like sweating, pallor, vomiting, breathlessness due to left ventricular failure (LVF), hypotension and disturbances in the rate and rhythm of the heart.

Clinical examination may be essentially normal, or may reveal a diastolic gallop and basal crepitations denoting LVF, or early evidence of shock in the form of pallor, sweating, hypotension, or evidence of arrhythmias. Any one or more of these features may be present.

There are a few points to be kept in mind in relation to the clinical diagnosis of AMI—

- In diabetics, elderly patients, and at times for no apparent cause, there may be little or no pain.
- In some patients, symptoms are perceived as gastrointestinal, with epigastric fullness, pain and vomiting.
- Acute MI may manifest with angina equivalent syndromes without pain. A recent large survey of 434,877 confirmed AMI patients reported that approximately 30% lacked chest pain on presentation, noting only the anginal equivalent complaints.[2] The most common anginal equivalent complaint is dyspnea.
- The geriatric patient may also present atypically with acute weakness (3–8%) and syncope.[3] Among the very elderly, anginal equivalent syndromes typically involve neurological presentations with disturbances in the mental status and stroke.
- Acute MI may occasionally present with the following clinical variants—
  - Acute LVF.
  - Acute shock of unexplained etiology.
  - Cardiac arrhythmias.

- ❖ Embolic complications, which draw attention to an underlying MI.

- ❑ Clinical examination may be perfectly normal with no change in the pulse or blood pressure (BP) even in the presence of an extensive infarction.
- ❑ A number of other noncardiac conditions can cause severe, protracted chest pain. To give just a few examples, chest pain may be due to musculoskeletal problems, esophageal spasm, a lower esophageal tear, acute abdominal problems, pulmonary embolism, pneumothorax, pleurisy, acute pericarditis and dissecting aneurysm of the aorta. *It is particularly important to exclude acute pericarditis and dissecting aneurysm of the aorta, as the use of thrombolytic therapy by mistake in either of these conditions can have disastrous consequences.*

ELECTROCARDIOGRAPHIC CHANGES

The ECG is an extremely important study in the evaluation of a patient with chest pain suspected of AMI. It provides critical information in a patient with STEMI, providing not only the diagnosis, but guiding management. It can also provide valuable information with regard to diagnosis and management in other coronary related events. Nevertheless, the ECG has its shortcomings and an awareness of these is of importance to physicians. To start with it, should be made clear that an AMI cannot be excluded even if the initial ECG is normal. The ECG should be repeated as changes may take hours or even a couple of days to manifest. Other shortcomings include the non-diagnostic interpretation, ECG changes in a NSTEMI (which may be nonspecific in nature) and the difficulty of ECG recognition of an isolated posterior or high lateral wall infarction.

ST-Elevation Myocardial Infarction

The earliest change in the STEMI is the presence of hyperacute T-waves which appear within minutes of stoppage of coronary blood flow through a coronary artery. This rapidly evolves into ST-elevation within 5–30 minutes.

Features of note in the elevated ST-segments in AMI are listed below—

1. ST-segment elevation in AMI tends to have a convex or obliquely flat morphology of the wave form. Patients with noninfarcted ST-elevation as with early repolarization or left ventricular hypertrophy related changes, tend to have concave morphology of the wave form. An analysis of ST-segment wave form confers specificity to the diagnosis of AMI in a person with chest pain.
2. Significant (2 mm rise) ST-segment elevation occurring in at least two anatomically oriented leads is an indication for fibrinolysis or PCI.
3. Left bundle branch block patterns, ventricular paced rhythms, left ventricular hypertrophy may obscure the typical ECG findings of AMI and may produce noninfarcted-ST-elevation, which may lead to mistakes in diagnosis.
4. ST-segment elevation can occur in acute pericarditis and in early repolarization. A wrong diagnosis of AMI can lead to dangerous therapy in a patient with pericarditis and unnecessary therapy in patient with ECG changes of early repolarization.
5. Q-waves generally develop 8–12 hours after a transmural infarct. They signify myocardial necrosis.
6. Right ventricular infarction and true posterior wall infarction can be missed on a 12 lead ECG. An additional lead V_4R evaluates the right ventricle and leads V_7 V_8 the posterior wall.

Non-ST-Elevation Myocardial Infarction

Patients with NSTEMI can present with various ECG abnormalities. These include symmetrically convex downward ST depression, inverted or biphasic T-waves. Unfortunately, the ECG findings in some instances initially appear normal. Regardless of the ECG presentation in NSTEMI patients, a diagnosis of MI in these patients can only be made if the troponins and creatinine phosphokinase (CPK), cardiac enzymes are clearly raised.

The importance of serial changes in the ECG, even if minor cannot be over-emphasized as these changes may constitute the only ECG evidence of MI. Also, ECG changes may occur well after the onset of symptoms; a diagnosis of MI should then be made in the presence of a typical clinical picture and corroborative evidence of myocardial necrosis in the form of raised cardiac enzymes particularly troponin I, T, CK, CK-MB. Posterior, high lateral and right ventricular infarcts are not easily detectable on the ECG and may evolve later.

Electrocardiography may also not always be helpful in the diagnosis of MI in patients with multiple previous infarcts, in LBBB, right ventricular paced patterns, the Wolff-Parkinson-White (WPW) syndrome and in patients on digitalis therapy. *The occurrence of a new or a fresh bundle branch block, particularly a fresh LBBB in a patient with ischemic cardiac pain should be taken as a sign of a fresh infarct.* In a patient with a pre-existing LBBB pattern or ventricular paced pattern, the presence of cardiac pain together with a loss of the normal discordance on the quasi-random signal-T (QRS-T) axis also suggests an underlying MI. Unfortunately, a lack of prompt ECG corroboration in some patients necessitates a delay in diagnosis and this delay may deprive a patient of thrombolytic or other interventional therapy to help salvage ischemic myocardium.

CARDIAC ENZYMES

The rise of cardiac specific enzymes troponin I and T in the blood are now considered the preferred biomarkers for the diagnosis of an acute myocardial infarct. A rise in absolute value of this troponin is observed in 2–3 hours in 80% of patients with MI thereby proving the diagnosis. Almost all patients will show a rise by 6–8 hours. It is however wise to do a 12-hour test as well, if clinical symptoms are highly suggestive and the earlier test for the troponins are not significantly elevated.

At 12 hours, the test is almost 100% sensitive for AMI;[4] a negative test at 12 hours in a patient presenting with chest pain effectively rules out AMI. What is more, a positive troponin test in patients with chest pain even with a nondiagnostic ECG and a negative CPK-MB independently confers the same prognosis as in patients with STEMI.[5] An important advantage of the troponin test over the CPK-MB (besides the greater sensitivity of the former) is that troponins remain elevated for as long as 7–8 days. It is important to do serial tests and document the rise and gradual fall of troponin levels after AMI.

It should be noted that troponin levels can rise in conditions other than MI. It is however the rise or fall of troponin values with one above the 99th percentile of the URL, coupled with clinical evidence of myocardial ischemia that differentiates AMI from other causes responsible for high troponin levels.

Others conditions causing a rise in troponin levels are shock from any cause, myocarditis, cardiomyopathies, congestive heart failure, pulmonary embolism, sepsis, renal failure, polytrauma, rhabdomyolysis. A rise may also be observed after extreme physical exercise. Causes of troponin T and I rise are listed in Box 1.

Box 1: Causes of serum troponin T and I elevations, including both acute coronary syndromes, noncoronary cardiac events, and noncardiac ailments

- Acute coronary syndrome or acute myocardial infarction
- Shock of any form (cardiogenic, obstructive, distributive)
- Myocarditis and myopericarditis
- Cardiomyopathies
- Acute congestive heart failure (pulmonary edema)
- Sepsis
- Pulmonary embolism
- Renal failure
- Sympathomimetic injections
- Polytrauma
- Burns
- Acute CNS event
- Rhabdomyolysis
- Cardiac neoplasm, inflammatory syndromes and infiltrative diseases
- Congenital coronary anomalies
- Extreme physical exertion

Abbreviation: CNS, central nervous system.

MANAGEMENT OF ST-SEGMENT ELEVATED MYOCARDIAL INFARCTION

Following admission to the ICU or the emergency department, a patient suspected of having AMI should be given complete bed rest, 300 mg of soluble aspirin (preferably chewed and swallowed), and 450 mg of clopidogrel. He is given oxygen, sublingual nitroglycerin (unless the systolic BP is <90 mm Hg) and given morphine or its derivatives for relief of pain and anxiety. An intravenous (IV) line is promptly secured (simultaneously sending blood for relevant investigations) and the patient is connected to an ECG monitor. A quick clinical examination is then performed with special reference to the cardiovascular and respiratory systems and a 12-lead ECG recorded. Points in diagnosis touched upon earlier are considered to determine whether the diagnosis of a suspected MI is probable or certain. Acute aortic dissection, acute pericarditis, and acute pleural and pulmonary problems need special consideration in the differential diagnosis. Complications of AMI are then carefully looked for—in particular LVF, arrhythmias and features of early shock; if present these are promptly treated.

If the ECG shows an ST-segment elevation of more than 1 mv in two or more contiguous leads, it signifies thrombotic occlusion of a coronary artery and the patient needs immediate reperfusion therapy. The diagnosis of an ST-segment elevated MI may at times be difficult as for example in the presence of LBBB of if the patient has a permanent pacemaker. A new LBBB pattern in the presence of symptoms of myocardial ischemia should be considered as an AMI and treated accordingly. In fact, patients with STEMI and LBBB derive greater benefit from reperfusion strategies compared to STEMI.[6]

For convenience, this chapter discusses management of STEMI in the following order. First, there is a brief discussion on the immediate supportive measures in AMI. It then discusses reperfusion strategies in STEMI. *It cannot however be sufficiently overstressed that reperfusion strategies should be promptly put into effect, as a matter of urgent priority as soon as a diagnosis of STEMI is made provided there are no contraindications*. Reperfusion strategies consist of the use of fibrinolytic drugs, PCI and surgical reperfusion (CABG).

Next is a brief discussion of the benefits of aspirin, antiplatelet drugs and anticoagulants used as adjuncts to fibrinolytic drugs and the use of PCI. The chapter then briefly mentions a few cardiac drugs that may be used later in the natural history of AMI. This is followed by a brief mention of the hemodynamic assessment of MI. Finally, there is a discussion on treatment of major complications.

Supportive Medical Therapy

Bed Rest

Complete bed rest is essential to start with. Most patients are nursed flat in bed; those with LVF need to be slightly propped up. The patient is encouraged to turn and move in bed from the very first day to minimize the risk of phlebothrombosis of the leg veins and hypostatic pulmonary congestion. In the absence of cardiac failure, arrhythmias, or shock, we encourage the patient to use a bedside commode to move his bowels. Most Indians find the bedpan an uncomfortable contraption; in fact, straining over a bedpan can prove disastrous and we tend to avoid its use as far as possible. If the patient is too ill to get out

of bed, and is unfamiliar with the bedpan, he is encouraged to move his bowels in bed into a large pad of cotton.

Relief of Pain

Severe unrelieved pain can lead to increasing anxiety, shock and may even trigger dangerous arrhythmias. The best drug to relieve both pain and anxiety in AMI is morphine. In patients with severe pain, morphine (if available) is given intravenously—2–4 mg being diluted and given slowly. Morphine is unfortunately not always easily available. The next best drug is buprenorphine, 0.3 mg intravenously. A careful watch is kept on respiration and blood pressure. 2 mg morphine (or 0.3 mg buprenorphine) may need to be repeated every 15–30 minutes till the pain is relieved, or there is evidence of toxicity. Severe vomiting, respiratory depression, or hypotension preclude its further use. In patients with mild or moderately severe pain, 15 mg morphine given subcutaneously suffices for pain relief. This can be repeated as necessary, although it is best not to use more than 60 mg morphine over 24 hours.

Morphine by relieving pain, anxiety and restlessness associated with AMI, results in a decrease in the myocardial oxygen demand. It also has a beneficial action in patients with pulmonary congestion due to LVF. This is because it produces vasodilatation and reduces the preload (particularly in those with excessive sympathetic activity), reduces the heart rate through increased parasympathetic activity and reduced sympathetic tone, and decreases the work of breathing by slowing respiration.

Hypotension following morphine can be countered by nursing the patient flat in bed or in the head-low position. A bolus or volume load of 150–200 mL dextrose saline generally suffices to raise the systolic pressure to above 100 mm Hg. The use of atropine 0.5–1 mg intravenously together with morphine counters the parasympathomimetic effect of the drug, particularly if bradycardia and a lowered systolic BP are present to start with. Vomiting is countered by the use of 25 mg intramuscular promethazine. Respiratory depression is surprisingly uncommon even with repeated doses of morphine in the presence of severe pain, or tachypnea due to pulmonary congestion. It should however be always watched for, especially in the aged and the feeble, and when present can be reversed by naloxone 0.1–0.2 mg intravenously. This dose can be repeated every 15 minutes till the respiration is no longer depressed.

Initially, morphine suffices to relieve anxiety. When pain is no longer present, anxiety should be relieved by benzodiazepine (diazepam 5 mg twice or thrice daily orally).

Establishing an Intravenous Line

An IV line is essential and is secured as soon as the patient is admitted, through an indwelling catheter in a peripheral vein. A 5% dextrose infusion is started at a very low flow rate through the IV line. This is a patency drip to be used for administering drugs. It is important to ensure that large quantities of fluids are not given intravenously (except for a specific purpose), for fear of inducing or aggravating pulmonary edema. If peripheral veins are unobtainable due to shock, a central line (either subclavian or internal jugular) is secured percutaneously. Blood samples for blood count, glucose, creatinine, CK, CK-MB, troponin I and T, serum glutamic-oxaloacetic transaminase (SGOT) and other relevant biochemical tests are collected when the IV line has been secured. It is best to avoid injections prior to sending blood CK levels to the laboratory, as intramuscular injections can by themselves cause a rise in the CK, and this can be misleading in diagnosis.

Oxygen

Oxygen at 2–4 L/minute is generally administered to a patient with a fresh MI for the first 24 hours. In a stable patient, without complications with an O_2 saturation well over 90%, oxygen perhaps confers no added advantage. Oxygen is however imperative in the presence of severe or persistent pain, in patients with an O_2 saturation less than 90%, or in the presence of breathlessness or shock, and in these situations it is given at a higher flow rate of 6 L/minute.

Electrocardiographic Monitoring

This is an extremely important aspect of critical care, as prompt detection of arrhythmias and their response to treatment can only be determined by continuous ECG monitoring. A high rate audiovisual alarm should be set at 110/minute, and a low rate signal at 50/minute. Monitoring of BP, temperature, urine output are other important features of critical care in MI.

Use of Nitrates

Nitrates are useful in the management of AMI provided there is no hypotension (systolic <100 mm Hg or a fall of >40 mm Hg from the baseline). In patients with severe or protracted pain, or when pain waxes and wanes, a slow infusion of nitroglycerin should be started at a rate of 5–10 μg/minute, the infusion rate being gradually increased every 10–15 minutes. There is no fixed optimal dose, but the infusion is titrated so that there is substantial pain relief or a drop in the systolic arterial pressure by 10–20%. In Indian patients, it is best not to exceed a dose of 50 μg/minute. The BP should not be allowed to fall below 100 mm Hg, and should be carefully monitored. Titration to total pain relief may be impossible in AMI. IV nitroglycerin infusions can be continued for 2–4 days if so required. Generally after 2–3 days the infusion is substituted by the application of nitroglycerin paste (1.5–2 inches) every 8 hours or by oral nitrates, e.g. isosorbide dinitrate 10 mg 8 hourly. It is best to avoid long-acting nitrates following AMI as titration of the dose is difficult. Patients who are stable from the start and whose pain has been virtually relieved by morphine, are treated in many units initially

with oral nitrates or local application of nitroglycerin paste, without prior use of IV nitroglycerin infusions. Flaherty and colleagues[7] have shown in a prospective randomized trial that the use of IV nitroglycerin for 48 hours followed by the use of nitroglycerin paste for 72 hours, enhanced postinfarction improvement of myocardial function in a scintigraphic study.

Nitrates are vasodilators. They reduce the venous return, the preload and therefore the workload on the heart. Myocardial oxygen demands are reduced, and this in turn leads to a reduction in myocardial ischemia. Nitrates also have a direct coronary vasodilator action and enhance blood supply to the ischemic myocardium. Both these modes of action contribute therefore to the relief of pain, and to preservation of ischemic myocardium. Patients in whom ST-segment elevation and myocardial ischemia are due to occlusive coronary artery spasm may experience prompt relief with IV nitroglycerin. A reduction in preload also leads to reduced filling pressures in the left ventricle, and may be of great benefit in patients with pulmonary congestion and edema due to left ventricular failure (LVF).

Nitrates are among the first line drugs used for symptomatic relief of myocardial ischemia; and in patients with MI who develop LVF. Despite these benefits, the Gruppo Italiano per lo Studio della Soprawivenza dell' Infarto Miocardico-3 (GISSI-3) and International Studies of Infarct Survival-4 (ISIS-4) trials failed to show a significant reduction in mortality from routine acute and chronic nitrate therapy.[8,9] The main side effect of nitrates is hypotension. Unfortunately, the prior presence of hypotension or a sharp hypotensive response soon after starting nitrates, at times limits the use of these drugs. They should be used with great caution in patients with inferior wall infarction as even a small dose may cause a precipitous fall in BP and heart rate—a reaction which can be promptly treated by IV atropine plus IV fluids. Nitrates, and in particular IV nitroglycerin are best avoided in patients with suspected right ventricular infarction. These patients often develop severe hypotension following their use because of inadequate right ventricular filling produced by vasodilatation. Hypotension induced by nitrates is dangerous; it reduces coronary perfusion, aggravates ischemia, and potentiates myocardial injury.

Headache is common with nitrates but only rarely is it severe enough to warrant discontinuation of the drug. Prolonged use of large doses has been known to cause methemoglobinemia. Elevated methemoglobin levels impair the oxygen-carrying capacity of the blood, and may increase myocardial ischemia.

Beta-blockers

Beta-blockers can be of benefit both in early AMI and as long-term therapy provided there are no contraindications to their use. Many act by causing a reduction in the heart rate, BP, myocardial contractility and hence in myocardial oxygen demand, thereby relieving chest pain and limiting infarct size. They may also help to reduce the incidence of post-infarction angina, ventricular arrhythmias, myocardial rupture and ventricular remodeling, thus reducing the overall mortality in AMI.[10]

Current evidence on the benefit conferred by the use of beta-blockers is a bit conflicting. In the Clopidogrel and Metoprolol in MI Trial-Second Chinese Cardiac 2 (COMMIT-CCS 2) trial of 45,852 patients with STEMI were randomized to receive treatment with metoprolol (3 IV injections of 5 mg each followed by oral 200 mg/day for up to 4 weeks) and placebo. Surprisingly, there was no difference in the primary endpoint of death, reinfarction, or cardiac arrest between the two groups. Based on these findings, the routine use of beta-blockers in the absence of hypertension is not recommended.[11]

On the other hand, in the CArvedilol Post-infaRct survIval COntRoL in Left Ventricular Dysfunction (CAPRICORN), a randomized placebo-controlled trial, there was clear benefit in the carvedilol arm after 1.3 years compared to the placebo both with regards to all-cause mortality and non-fatal MI.[12] This study supports the claim that beta-blocker therapy after acute MI reduces mortality irrespective of reperfusion therapy or angiotensin-converting enzyme (ACE) inhibitor use.

Notwithstanding conflicting evidence (so frequent in critical care medicine), it is perhaps best not to use beta-blockers on a routine basis soon after AMI particularly in massive infarcts which are likely to be associated with or followed by LVF. Beta-blockers however help in the following circumstances—

- In patients whose infarction is complicated by persistent or recurrent ischemic cardiac pain, particularly when associated with tachycardia.
- In patients with marked sinus tachycardia, particularly when associated with anxiety and hypertension.
- In patients with tachyarrhythmias refractory to the usual antiarrhythmic drugs. In fact, *tachyarrhythmias related to hyperadrenergic states in AMI including ventricular tachycardia (VT) at times respond best to the judicious use of beta-blockers*.
- In patients who have been beta-blocked prior to infarction, a sudden withdrawal of the drug may produce severe tachycardia. In such cases, beta-blockers should be continued in smaller doses.

Contraindications Beta-blockers are contraindicated in patients with LVF, hypotension (systolic BP <100 mm Hg), bradycardia (heart rate <60–65/minute) or heart block. They are also contraindicated in a patient with a history of asthma, or of chronic airways obstruction.

Mode of use The beta-blocker most commonly used in AMI is metoprolol given intravenously in three 5 mg bolus doses to a total of 15 mg. The patient is observed for 5 minutes after each bolus dose. No further dose is given if the heart rate falls below 60 beats/minute or systolic BP falls to less than 100 mm Hg or the PR interval is prolonged beyond 0.24 second,

Box 2: Indications for using beta-blockers in acute myocardial infarction

- Within the first 4–6 hours after AMI (early use), provided no contraindications exist
- *Later in the natural history of AMI*
- In patients with marked sinus tachycardia
- In patients with marked sinus tachycardia (not due to left ventricular failure), particularly when associated with anxiety and hypertension
- In patients in whom infarction is complicated by persistent or recurrent ischemic pain, especially if associated with tachycardia and/or hypertension
- In patients with tachyarrhythmias refractory to conventional antiarrhythmic drugs
- In patients who have been beta-blocked prior to AMI

Abbreviation: AMI, acute myocardial infarction.

or basal crackles or a diastolic gallop appear. If the patient remains hemodynamically stable after the last bolus dose for 30 minutes, metoprolol is continued orally, 50 mg 12 hourly. The dose needs to be titrated to ensure that hypotension, bradycardia or LVF do not occur. The drug is also promptly stopped if bronchospasm occurs.

The CAPRICORN study suggests that carvedilol (a beta-blocker) given postinfarct gives a clear benefit with regard to mortality, reinfarction and death Box 2.

Interventional Therapy

Fibrinolysis

Numerous clinical trials provide overwhelming evidence that fibrinolytic agents administered early in the course of AMI reduce infarct size, preserve left ventricular function and substantially reduce mortality in ST elevated MI.[9-11]

The benefit occurs from the ability of fibrinolytic agents to lyse clots within a coronary artery and thereby re-establish perfusion of blood to the affected area of the myocardium. The Fibrinolyitc Therapy Trialists' Collaborative Group (FTT)[13] showed that mortality in Q-wave infarction is reduced by 25–30%, if fibrinolytic therapy is instituted in patients with either ST-segment elevation or new bundle branch block up to 12 hours, and possibly as much as 18–24 hours after the onset of symptoms. The maximum benefits were observed in patients with anterior ST-segment elevation but patients with inferior ST-segment elevations also benefit. Patients with Q-wave infarction, who are at the greatest risk, have the greatest benefit. The sooner treatment is instituted, the better the results.

This is beautifully illustrated below by a study of pooled findings from 22 randomized-controlled trials of thrombolyitc therapy published between 1983 and 1993.[13] This study noted the following—

Time when thrombolysis started	Additional lives saved per 1,000 people treated with thrombolytics compared with 1,000 people treated with standard therapy
In the first hour	65
In the second hour	37
In the third hour	26
Between 3 and 6 hours	26
less than 12 hours	18
Between 12 and less than 24 hours	9

The imperative need to use fibrinolytic agents as early as possible in patients with AMI where fibrinolytic therapy is indicated, and where no contraindications to this therapy exist, is clearly evident.

Indications When a patient with AMI (suspected or proven) is referred to the ICU, the immediate question is to determine whether the patient is a candidate for thrombolytic therapy. The following criteria for the use of thrombolytic agents in AMI must be considered—

- Chest pain for more than 30 minutes, consistent with AMI.
- Electrocardiography changes showing—
  - ST-segment elevation more than 1–2 mm in at least two contiguous frontal leads (leads I, aVL, II, III, aVF) or two precordial leads (the V leads) or in STEMI with or without Q-waves. It is to be noted that a right ventricular infarct may manifest with an elevated ST in V_4R, and a tall R in V_4R. It is often associated with elevated ST in leads II, III, aVF. The ST deviation in all patients should be measured 0.4 second after the J point, using the PQR segment as the isoelectric line.
  - New or presumed new LBBB, because this invariably denotes an acute anterior myocardial infarct.
- Although bleeding complications following fibrinolysis are more frequent in patients more than 75 years, it is generally accepted that age is not an absolute bar to fibrinolysis, provided the benefit that accrues is judged to be greater than the risk.
- The therapy to be effective should be given early in the course of AMI. It is most beneficial if given within 6 hours of the onset of pain (or pain equivalent). It is less beneficial but is still used between 6 hours and 12 hours of pain. It may be used between 12 hours and 24 hours after onset of pain, particularly if pain persists, but with decreasing benefits.
  Fibrinolytic therapy is not indicated in patients with unstable angina, in myocardial infarcts with ST depression or nonspecific ST changes, i.e. in NSTEMI.
- There is, however, a subset of patients eligible for thrombolysis even though they do not present either with ST-elevation or LBBB. These are patients with—
  - True posterior wall infarction that may have a tall R in V_1 and V_4R or present with marked ST-segment

Box 3: Contraindications to fibrinolytic therapy

- *Absolute—*
  - Bleeding diathesis or chronic liver disease with portal hypertension
  - Active recent internal bleeding
  - Cerebrovascular accident in the recent past (3 weeks)
  - Recent trauma, head injury or major surgery
  - Aortic dissection
  - Proliferative hemorrhagic diabetic retinopathy
  - Uncontrolled severe hypertension
  - Known presence of aneurysm or arteriovenous malformations
- *Relative—*
  - Serious organic disease associated with increased risk of bleeding or embolization
  - Poorly controlled hypertension
  - Prolonged cardiopulmonary resuscitation
  - Pregnancy or postpartum or menstruating women

depression in V_1 to V_4 which represents a posterior current of injury. The infarction is generally due to an occlusion of the circumflex artery, or occlusion of the posterior descending branch of the right coronary artery.

- Anterior MI, which in the very early phase may show hyperacute giant T-waves without ST-segment elevation.

Contraindications The major danger in the use of fibrinolytic therapy is bleeding. Contraindications to its use are outlined in Box 3.

These include a bleeding diathesis, an active peptic ulcer, active recent internal bleeding, history of a cerebrovascular accident in the recent past (3–4 weeks), recent major surgery, recent intracranial or spinal surgery, recent trauma, recent head injury, severe uncontrolled hypertension (diastolic >110 mm Hg), known presence of an aneurysm or an arteriovenous malformation, aortic dissection and proliferative diabetic retinopathy. Relative contraindications include a recent arteriotomy or puncture of a major vessel, poorly controlled hypertension, recent organ biopsy (2–3 weeks), recent obstetric delivery and recent protracted cardiopulmonary resuscitation.

Risks of Fibrinolytic Therapy

Bleeding Bleeding generally occurs from puncture wounds (arteries and veins). However, the general fibrinolysis caused by thrombolytic agents can occasionally cause catastrophic bleeding leading to death. The most dreaded of all complications is an intracranial bleed.

Reperfusion arrhythmias Reperfusion arrhythmias are occasionally observed in patients during or immediately after fibrinolytic therapy. These take the form of accelerated idioventricular rhythm and frequent ventricular ectopics. Rarely ventricular fibrillation may occur abruptly. Marked sinus bradycardia and hypotension may be observed following reperfusion in inferior wall infarction. There is considerable interest in the physiopathology of reperfusion arrhythmias. Metabolites accumulate in the ischemic and injured myocardium following occlusion of a coronary vessel. A wash-out of these metabolites following reperfusion results in electrical and chemical gradients across cell membranes, resulting in arrhythmias.[14]

Assessing the Efficacy of Fibrinolytic Therapy

Fibrinolytic therapy can be gauged to have succeeded, if there is relief of pain, a reduction in ST-elevation by about 50%, and by an improved hemodynamic state. The occurrence of an accelerated idioventricular rhythm after fibrinolysis generally denotes successful reperfusion. Persistent pain, an unimproved hemodynamic state, with no change in the elevated ST-segments, and even perhaps an extension of the infarct size, point to a failure of fibrinolytic therapy.

Fibrinolytic Drugs

Streptokinase (SK) was the first lytic agent used in MI; it has now been largely replaced by tissue plasminogen activator (tPA), which is more fibrin selective and has a higher early coronary patency rate (70–80%).[15] Reteplase (rPA) is a deletion mutant of tPA but its use has no added advantage compared to tPA.[16] Tenecteplase-tPA (TNK-tPA) is a genetically engineered tPA with a longer half-life; it is resistant to plasminogen activator inhibitor 1, and has increased fibrin specificity. TNK-tPA is given as a single bolus which results in coronary flow rates identical to those seen with accelerated tPA, with equivalent 30-day mortality and bleeding complications.[17] An ideal fibrinolytic agent has not yet been developed. Such an ideal drug should have greater fibrin specificity, should remain in the circulation for a longer time and should be even more resistant to protease inhibitors than agents in current use. The newer agents have by and large equal efficacy but are more easily administered and therefore have gained greater popularity. It must be noted that although tPA and its newer derivatives are superior lytic agents compared to SK, the latter continues to be used in our country and in other poor developing countries of the world because of its low cost.

Dosage Streptokinase is administered in a continuous IV infusion of 1.5 million units over 1 hour. The administration of SK occasionally causes anaphylactic reactions which range from itching and urticaria to bronchospasm and severe hypotension. If severe, the drug is stopped and the anaphylactic reaction countered by IV hydrocortisone.

Tissue plasminogen activator Administration of tPA follows an accelerated regime consisting of a 15 mg bolus, 0.75 mg/kg (up to 50 mg IV) over 30 minutes and then 0.5 mg/kg (up to 35 mg) over the next 60 minutes.

Table 1: Weight adjusted dosing of tenecteplase

Patient weight (kg)	*Tenecteplase (mg)*	*Volume of tenecteplase to be administered (mL)*
<60	30	6
60–69	35	7
70–79	40	8
80–89	45	9
≥90	50	10

Reteplase is given as two 10 U boluses 30 minutes apart.

Tenecteplase is dosed-based on weight and is given as a single-bolus injection over 5 seconds (Table 1). This drug is not compatible with dextrose, and therefore, should not be given in the same IV line. Lines containing dextrose should be flushed before and after administration.

Fibrinolytic therapy is followed by the use of heparin. The use of heparin, other anticoagulants as adjunctive therapy is considered later—following the discussion on Primary Coronary Angioplasty.

Re-use of fibrinolytic therapy If fibrinolytic therapy fails to afford relief, a rescue angioplasty is generally indicated. If, however, facilities for a rescue angioplasty are lacking, as is so in a number of critical care units, thrombolysis may be attempted again. The following points need to be stressed—

- If SK is used for initial fibrinolysis, it should not be used again as it can cause severe anaphylaxis.
- Re-use fibrinolytic therapy should therefore always be with tPA. If prior fibrinolytic therapy was given 12 hours back for tPA, or 24 hours back for SK, 25–50% of the usual dose of tPA is administered. If more time has elapsed after initial therapy, the full dose of tPA can be given.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Primary percutaneous coronary intervention if performed early and with sufficient expertise has been shown to be superior to the use of fibrinolytic drugs. The major advantages of PCI over fibrinolytic therapy are the achievement of a higher rate of normal blood flow [thrombolysis in MI (TIMI) grade 3],[18] a reduced risk of intracranial hemorrhage and the ability to stratify risk with regard to the nature, distribution and extent of coronary artery disease. There are a few points in favor of PCI vis-à-vis fibrinolytic therapy. These are—

- Percutaneous coronary intervention ensures a reperfusion rate of 90–95% compared to the reperfusion rate of 70–80% with the best available fibrinolytic therapy.
- The reocclusion rate in patients undergoing fibrinolytic therapy is higher than those undergoing percutaneous transluminal coronary angioplasty (PTCA).
- Percutaneous transluminal coronary angioplasty is feasible in all patients with AMI including those who are not eligible for fibrinolytic therapy.

Points against PCI also need mention—

- The logistic difficulty of performing a PTCA preferably within 4 hours, or at most within 12 hours of the onset of AMI—a time period when its efficacy is proven; also to be effective, PCI should be within 90 minutes of reaching the hospital; door to balloon time should be within 90 minutes (medical contact to balloon).
- The unavailability of the necessary equipment, expertise, experience and logistic support in many centers in developing countries.

Several randomized trials have suggested the superiority of PCI over fibrinolytic therapy in several subsets of AMI patients at higher risk.[19] The largest of these trials is the GUSTO-IIb Angioplasty Substudy, which randomized 1,138 patients and showed at the end of 30 days a small to moderate clinical benefit in the combined primary endpoint of death, nonfatal reinfarction, and nonfatal stroke in the patients treated with PTCA compared to patients treated with tPA.[20]

Recent meta-analysis comparing direct PTCA with fibrinolytic therapy suggests lower mortality and lower rates of reinfarction in patients treated with PTCA.

However, more important than the method of revascularization is the time taken to revascularize. PCI is the preferred method for revascularization in STEMI only if the door to balloon (or medical contact to balloon) time for PCI is less than 90 minutes.[21] Similarly, if fibrinolytic therapy is offered to a patient with STEMI the door-to-needle (or medical contact to needle) time ideally should be 30 minutes.[22] Timely reperfusion is the key to success—reducing or limiting infarct size, preserving LV function and increasing survival.[23,24]

Special indications for PCI are—

- In patients in whom fibrinolytic therapy is contraindicated.
- Failure of fibrinolytic therapy.
- In patients with severe ischemic cardiac pain, with a marked rise in the cardiac enzymes or in those with a possible stuttering infarction and yet with no typical ECG features of MI.
- In a patient in whom acute pericarditis or a dissecting aneurysm of the aorta cannot be ruled out. A coronary angiography followed by an angioplasty if there is occlusion of a major artery can be done.
- In patients who are hemodynamically unstable or in cardiogenic shock.
- In patients who have had coronary artery bypass surgery in the past and in patients who have had a prior myocardial infarct.
- In elderly patients well over 75 years in whom the risk of bleeding from fibrinolytic therapy is significant.

Percutaneous coronary angioplasty in AMI is always followed by stenting the involved artery.

The Primary Angioplasty in MI (PAMI) stent trial (a large randomized trial) was carried out to determine if routine stenting in MI could reduce angiographic restenosis and

improve clinical outcomes when compared to balloon angioplasty alone. There was no difference in mortality in the two groups at 6-months but there was improvement in target driven revascularization and improvement in angina in stented patients compared to balloon angioplasty alone.[25] Stenting however remains a universal policy in patients with AMI treated by PCI. In most instances a drug eluting stent is preferred to a bare metal stent although there are no definitive clinical trials to support this preference.

SURGICAL REPERFUSION (CORONARY ARTERY BYPASS SURGERY)

Coronary artery bypass surgery has indeed a very small place in the management of AMI. It is indicated under the following conditions—

- When coronary dissection with occlusion develops during cardiac catheterization, coronary angiography or during PTCA.
- Surgical reperfusion is to be considered in a small subgroup of patients who are undergoing or have completed fibrinolytic therapy, but who continue to have ischemic pain and are hemodynamically unstable. Rescue angioplasty is to be preferred but if this fails or is not feasible, or if the angiography shows left main disease or multivessel disease, emergency surgical revascularization is of benefit. Good centers report a low mortality and morbidity.[26,27]
- Surgical reperfusion after an infarct has just fully evolved is invariably unsafe, unwise and contraindicated. However, in some patients, infarction appears to occur in a stuttering manner over a period of days producing increasing hemodynamic instability and shock. Revascularization in these patients, although fraught with danger, may at times be successful and followed by recovery.

Adjunctive Therapy

The purpose of fibrinolytic therapy or PCI is: (1) to restore blood flow to the thrombosed infarct related artery; (2) to limit microvascular damage and reperfusion injury. The latter is accomplished with the use of adjunctive therapy which is now described in the section below.

Adjunctive Therapy to Primary Percutaneous Coronary Intervention or to Fibrinolytic Therapy

Aspirin Aspirin is an effective cheap antiplatelet drug with relative low toxicity. The drug has been shown to reduce mortality in AMI to the same degree as fibrinolytic therapy. When used together with fibrinolytic therapy, its effect is additive. The drug should always be administered in all acute coronary syndromes—STEMI, NSTEMI, unstable angina as soon as possible. Contraindications to its use are active peptic ulcer disease, history of intolerance to the drug.

Thienopyridine These antiplatelet drugs inhibit both the activation and aggregation of platelets. Clopidogrel is the drug most frequently used. Prasugrel is a more recent thienopyridine and is now easily available in India. Clopidogrel is a pro-drug which is converted to its active metabolite in the liver via the cytochrome p450. This metabolite prevents activation of the GP IIb/IIIa receptor complex and reduces platelet aggregation. A loading dose of 300–600 mg inhibits platelets within 2 hours, whereas a dose of 75 mg achieves inhibition of platelets in 24–48 hours. Peak effect is at 6 hours after a loading dose of 300–600 mg and 5–7 days with a loading dose of 50–100 mg.[28]

The large Clopidogrel as Adjunctive Reperfusion Therapy-TIMI 28 (CLARITY TIMI-28) study[29] randomized 3,491 STEMI patients to clopidogrel (300 mg loading dose + 75 mg daily) and placebo. The study showed: (1) the efficacy of clopidogrel to maintain infarct artery patency; (2) prior reuse of clopidogrel in patients who underwent PCI resulted in a significant reduction in cardiovascular death, MI or stroke at 30 days without causing excessive bleeding.[30] Clopidogrel is therefore administered in a dose of 300–600 prior to PCI even if there is the possibility that the patient may require coronary artery bypass surgery in the near future.

Prasugrel, a more recent thienopyridine is also a pro-drug which acts only after its conversion to its active metabolite. It is a more powerful drug compared to clopidogrel in that it inhibits platelet aggregation to a greater degree. A dose of 60 mg inhibits platelet aggregation in 30 minutes, the peak effect being observed in 4 hours.[31] The side effect of both clopidogrel and prasugrel is bleeding, the rate of major bleeding episodes being higher with use of prasugrel. Prasugrel should not be used in patients with a history of transient ischemic attacks and/or stroke, in patients more than 75 years and in patients with a body weight less than 60 kg.

Currently both aspirin and clopidogrel (or prasugrel) are given to all patients prior to PCI as mentioned above. On the basis of data provided by the COMMIT-CCS-2 study, all patients would benefit from the addition of clopidogrel to aspirin regardless of whether they do or do not undergo reperfusion therapy. The duration of clopidogrel use following AMI has not been defined.

Ticagrelor Ticagrelor is the new antiplatelet drug used in the treatment of both, NSTEMI and STEMI. The recommended dosage is 180 mg—loading dose followed by 90 mg twice daily as maintenance dose (also see Chapter Unstable Angina).

Glycoprotein IIb/IIIa receptor antagonists Glycoprotein IIb/IIIa receptor antagonists inhibit the final common pathway of platelet aggregation by blocking cross linking of aggregated platelets. Prior to the use of clopidogrel and aspirin as antiplatelet therapy the efficacy of abciximab (a glycoprotein IIb/IIIa receptor antagonist) in patients with STEMI who underwent primary PCI was established. Recent trials have questioned whether abciximab when added to aspirin and clopidogrel offers any additional benefit in patients with STEMI.[32]

Current guidelines suggest that when a STEMI patient is treated with clopidogrel and aspirin plus an anticoagulant such as unfractionated or low molecular weight heparin, the glycoprotein IIb/IIIa inhibitor at the time of PCI may benefit but cannot be recommended for routine use.[22]

Anticoagulants Following fibrinolytic therapy, it is important to administer heparin to diminish reocclusion after successful reperfusion. Sixty units/kg up to a maximum of 4,000 units are given as a bolus followed by an infusion rate of 12 U/kg up to a maximum of 1,000 U/hour, the infusion being titrated to keep partial thromboplastin time (PTT) at two to two and half times the control. Heparin should be continued for 48 hours.

For patients undergoing PCI who have already received aspirin and clopidogrel, both unfractionated heparin and bivalirudin can be used as anticoagulants. Bivalirudin is a thrombin inhibitor and is administered in a bolus injection 0.75 mg/kg followed by an infusion at 1.75 mg/kg per hour for the duration of PCI. *Bivalirudin* is the anticoagulant of choice in patients with a history of heparin induced thrombocytopenia. It is as effective as heparin and its use is less often complicated by bleeding episodes.

Enoxaparin is a low molecular weight heparin with proven efficacy in patients with STEMI who have received fibrinolytic therapy or are undergoing PCI.[33] It is given by injection subcutaneously in a dose of 1 mg/kg every 12 hours. Patients more than 75 years or who have renal dysfunction need a reduced dose of 0.5–0.75 mg/kg every 12 hours.

There are many who prefer the use of low molecular weight heparin (LMWH) to unfractionated heparin following fibrinolytic therapy and as an anticoagulant before, during and after PCI.

Fondaparinux is a Factor XA inhibitor which can be used in place of low molecular weight heparin (LMWH). It is given subcutaneously in a dose 2.5 mg once daily. It has proven efficacy when used in patients with STEMI. However, the use of fondaparinux in STEMI patients undergoing PCI has been associated with an increased incidence of catheter related thrombosis.[34] If fondaparinux is used in the above situation, fractionated heparin should also preferably be administered.

Medical supportive therapy during the early phase of AMI has already been discussed. It now remains to briefly mention the role of other drugs in AMI.

Calcium antagonists Both verapamil and diltiazem are best avoided immediately after a STEMI. They may be tried in post-MI angina or in slowing the ventricular rate in atrial fibrillation when beta-blockers are ineffective or contraindicated. Calcium channel blockers have a negative inotropic effect on the heart.

Angiotensin-converting enzyme inhibitors These are avoided during the immediate phase of STEMI but may be of benefit after a few days. ACE inhibitors are of particular use in patients with clinical evidence of heart failure, in those with an ejection fraction less than 40%, and in those with a history of previous MI. If captopril is used, it is given in a dose of 6.25 mg orally twice daily, titrating the dose slowly to 25 mg twice daily, provided there is no significant hypotension, nor a rise in the serum creatinine. Lisinopril, enalapril or ramipril could also be used in appropriate titrated doses. One should aim to reduce the systolic BP by approximately 10% in normotensive individuals and by 30% in hypertensive individuals. ACE inhibitors should not be used when the systolic pressure is less than or equal to 100 mm Hg.

Box 4: Indications for hemodynamic monitoring in acute myocardial infarction (AMI)

- Cardiogenic shock
- Refractory pulmonary edema due to left ventricular failure
- Suspicion of right ventricular infarction or pulmonary embolism
- Ventricular septal rupture or papillary muscle rupture causing mitral regurgitation
- When using combination of inotropes and vasodilators
- Suspicion of cardiac tamponade

The heart outcomes prevention evaluation (HOPE) trial[35] randomized 9,297 patients with documented vascular disease or those at high risk for atherosclerosis to treatment with ramipril (target dose 10 mg/day), or placebo. There was a significant 22% reduction in the combined endpoint of cardiovascular death, MI, and stroke observed in those treated with ramipril. Also, an improved survival was additive to the benefits of aspirin and beta-blockers.[35]

Angiotensin-converting enzyme inhibitors reduce the afterload and thereby the work of the heart. There is probably also a limitation of LV dysfunction and LV remodeling that often follows in AMI. An observed reduction in ischemic events is probably related to reduced workload on the heart.

Intravenous magnesium It has been suggested that IV magnesium is an inexpensive and relatively safe means of reducing serious arrhythmias and deaths from AMI.[36] Eight mmoL of magnesium sulfate is given intravenously over 5 minutes, followed by 65 mmoL over 24 hours. It probably acts by preserving myocardial tissue as well as by suppressing arrhythmias.

Lipid-lowering agents Statins decrease the rate of ischemic events in patients with coronary artery disease.[37] A high-dose statin administration (as a loading dose) has been advocated prior to PCI for STEMI. The STATIN STEMI trial appears to endorse the use of this therapy.[38] Currently, this therapy is not considered essential prior to PCI. However, all patients with the acute coronary syndrome should be discharged on a statin prior to discharge.

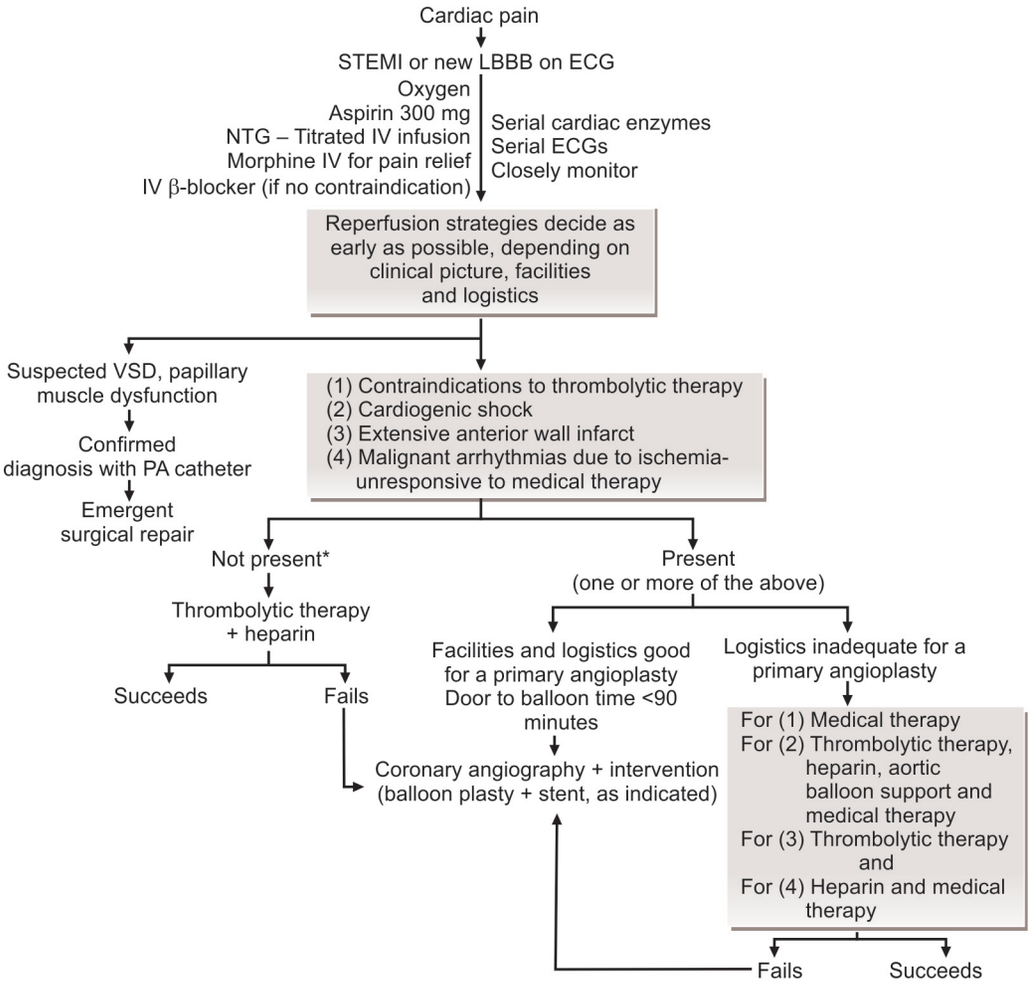
An algorithm for the management of STEMI is given in Flowchart 1.

HEMODYNAMIC ASSESSMENT OF ACUTE MYOCARDIAL INFARCTION

With experience, most patients can be assessed satisfactorily with regard to their hemodynamic status by clinical methods and by noninvasive monitoring (Box 4). We reserve invasive monitoring with a Swan-Ganz catheter for the following situations—

- Cardiogenic shock.
- Refractory pulmonary edema due to LVF.

Flowchart 1: Algorithm for the management of ST-elevation myocardial infarction (STEMI)


Cardiac pain
STEMI or new LBBB on ECG
Oxygen
Aspirin 300 mg
NTG – Titrated IV infusion
Morphine IV for pain relief
IV β-blocker (if no contraindication)
Serial cardiac enzymes
Serial ECGs
Closely monitor
Reperfusion strategies decide as early as possible, depending on clinical picture, facilities and logistics
Suspected VSD, papillary muscle dysfunction
Confirmed diagnosis with PA catheter
Emergent surgical repair
(1) Contraindications to thrombolytic therapy
(2) Cardiogenic shock
(3) Extensive anterior wall infarct
(4) Malignant arrhythmias due to ischemia-unresponsive to medical therapy
Not present*
Thrombolytic therapy + heparin
Succeeds
Fails
Present (one or more of the above)
Facilities and logistics good for a primary angioplasty Door to balloon time <90 minutes
Logistics inadequate for a primary angioplasty
For (1) Medical therapy
For (2) Thrombolytic therapy, heparin, aortic balloon support and medical therapy
For (3) Thrombolytic therapy and
For (4) Heparin and medical therapy
Coronary angiography + intervention (balloon plasty + stent, as indicated)
Fails
Succeeds

*Some well-equipped units would prefer primary angioplasty to thrombolytic therapy (if door to balloon time <90 minutes).

Abbreviations: STEMI, ST-elevation myocardial infarction; LBBB, left bundle branch block; ECG, electrocardiography; NTG, nitroglycerin; IV, intravenous; VSD, ventricular septal defect; PA, pulmonary artery.

- Suspicion of right ventricular infarction or pulmonary embolism.
- Ventricular septal rupture, or papillary muscle rupture causing mitral regurgitation.
- Suspicion of cardiac tamponade.

TREATMENT OF MAJOR COMPLICATIONS

1. *Cardiogenic shock* Shock following AMI has been discussed separately (described in Chapter Cardiogenic Shock). The present trend is to restore some stability to the hemodynamic state so that the patient can have a coronary angiography done, and if possible a rescue angioplasty performed. These procedures should be carried out with the help of an aortic balloon assist device.
2. *Left ventricular failure* This has been discussed separately.
3. *Congestive cardiac failure* The principles of management have been dealt with in a separate chapter.
4. *Arrhythmias* Arrhythmias need to be promptly detected and controlled. Ventricular arrhythmias are particularly common during the first 24 hours. Some units prefer to start prophylactic IV lidocaine in all patients with fresh infarcts. Others prefer to treat arrhythmias as and when they arise.
5. *Postinfarction angina* Postinfarction angina requires prompt return to the ICU and the administration of IV nitroglycerin and restarting of IV heparin. An aggressive approach is important because of the risk of reinfarction and sudden death. This is particularly true in patients with a NSTEMI where the absence of marked ECG changes to start with may lull the physician into complacency. The use of diltiazem 30–60 mg 8 hourly may reduce the immediate short-term risk of reinfarction and death in these patients.[39]
6. *Persistent postinfarction angina* always needs to be investigated by a coronary angiography. Further management

(whether an angioplasty or surgical reperfusion through coronary artery bypass surgery) depends on the angiographic findings.

7. *Right ventricular infarction* Right ventricular infarction should always be thought of in patients with inferior wall infarction who develop hypotension with poor perfusion, whose central venous pressure (CVP) is raised, and in whom the lung fields are relatively clear. An ECG shows an elevated R and an elevated ST-segment in V_4R; this change may disappear within 24 hours. Bradyarrhythmias may occur, necessitating the use of a temporary pacemaker. Echocardiography reveals right ventricular dilatation, wall motion abnormalities and often left ventricular dysfunction. Invasive hemodynamic studies through a S-G catheter reveal a raised right atrial pressure, a raised right ventricular end—diastolic pressure, and a normal to low pulmonary artery diastolic or pulmonary capillary wedge pressure. The cardiac output is reduced. These patients should be carefully volume loaded in spite of an increased CVP, to increase the left ventricular filling pressures and cardiac output. They invariably need inotropic support with dobutamine and dopamine as well.
8. *Pericarditis* Pericarditis generally occurs after 48 hours causing pericardial pain, and fever. The pain is worse on lying supine, breathing deeply, and swallowing. It is relieved by sitting up; a friction rub is generally audible. It is often mistaken for an extension of the infarct or for postinfarction angina. In mild cases, it is relieved by nonsteroidal anti-inflammatory agents. When severe, it is relieved by dexamethasone 4 mg intravenously 8 hourly, tapered off within a week. Rarely, pericardial effusion is large enough to cause a cardiac tamponade; this necessitates a pericardial paracentesis. Heparin should be withheld in the presence of pericardial effusion.
9. *Rupture of the interventricular septum* Septal rupture is characterized by the sudden appearance of a pansystolic murmur, generally best heard in the fourth left intercostal space, close to the left sternal border or midway between the left sternal border and the apex. Biventricular failure always follows. The diagnosis can be confirmed by two-dimensional (2D) Doppler echocardiography. An S-G catheter will help to demonstrate a step-up of oxygen saturation from the right atrium to the right ventricle (due to a left to right shunt at the ventricular level). Immediate management is concerned with restoring hemodynamic stability. Afterload and preload are reduced by a slow infusion of IV nitroprusside, and inotropic support is provided by dopamine or dobutamine to maintain the systolic BP 90–100 mm Hg. An intra-aortic balloon pump is used to help to stabilize the circulation. Ventilatory support is often required. *It is important to opt for quick surgical repair, and it is wrong to wait for days or weeks before undertaking surgery*. Invariably, delay results in a progressive worsening of the hemodynamic state, and the evolution of multiple organ failure. Once the latter complication ensues, surgery, even if attempted, is almost always unsuccessful.
10. *Rupture of a papillary muscle* Papillary muscle rupture produces a pansystolic murmur at the apex due to severe mitral incompetence. It needs to be distinguished from a ruptured interventricular septum. There is no step-up in the oxygen saturation from the right atrium to the right ventricle in this condition, and large regurgitant V-waves are observed in the pulmonary wedge tracing. A papillary muscle rupture leads to LVF with pulmonary edema together with failure of forward flow and impaired tissue perfusion. Management is on the same lines as for intraventricular septal rupture. A combination of afterload and preload reduction by using sodium nitroprusside, together with inotropic support with dopamine, is necessary. Preload may need to be further reduced by furosemide. An aortic balloon pump is to be used to help restore a semblance of hemodynamic stability. Urgent surgical repair should be considered in these patients.
11. *Myocardial rupture* Rupture of the free wall of the ventricle typically occurs 3–5 days after an infarction. It usually presents with rapid hypotension and pericardial tamponade progressing quickly to electromechanical dissociation and death. Patients are almost never salvageable. If there is a comparatively slow leak of blood into the pericardium, time for possible rescue measures may be available. The diagnosis of tamponade should be made on clinical grounds. Echocardiography, if available, can be extremely useful. Treatment consists of emergency pericardiocentesis, infusion of fluids, inotropic and vasopressor support, ventilatory support and rapid transfer to the theater for surgical repair. We have never had the good fortune of salvaging a patient with rupture of the ventricular wall following an MI.
12. *Embolic complications* Embolic complications can arise from mural thrombi that may form within the ventricle over the infarcted area. Clinical features depend on the site of embolization. Neurological deficits due to emboli in the cerebrovascular circulation may at times be the presenting feature of an underlying MI. Anticoagulation is recommended in such patients. Rarely a saddle block due to an embolus straddling the aortic bifurcation, produces a loss of blood supply to both lower limbs. Removal of the obstructing clot through a Fogarty's catheter introduced through the femoral artery should be promptly done; this is followed by anticoagulation (Box 5).
13. Pulmonary embolism. Pulmonary emboli can arise from thrombi within the right atrium or right ventricle or from thrombi within the deep veins. This complication worsens pregnosis (see Chapter Pulmonary Embolism).

MYOCARDIAL STUNNING OR HIBERNATION

These entities have attracted considerable attention. In myocardial stunning, systolic dysfunction persists for a time after an ischemic episode even though reperfusion has been

Box 5: Major complications of acute myocardial infarction

- Cardiogenic shock
- Left ventricular failure
- Congestive cardiac failure
- Arrhythmias
- Postinfarction angina
- Right ventricular infarction
- Pericarditis
- Rupture of interventricular septum
- Rupture of a papillary muscle
- Myocardial rupture
- Embolic complications
- Pulmonary embolism

established. It can occur after thrombolysis in AMI and after cardiopulmonary bypass. A hibernating myocardium is poorly contractile but still viable area of myocardium due to poor coronary blood flow. The myocardial dysfunction improves when coronary blood flow to the area is re-established.

DURATION OF INTENSIVE CARE

An uncomplicated acute myocardial infarct can be transferred out of the ICU after 2 days. An AMI with complications should stay till such time as intensive care is necessary. The need for hemodynamic monitoring, use of inotropes or of drugs to reduce afterload or preload and close nursing supervision necessitate a longer stay in the ICU.

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CHAPTER 22

Acute Left Ventricular Failure with Pulmonary Edema

INTRODUCTION

Acute left ventricular (LV) failure with pulmonary edema is always associated with a marked increase in the LV end-diastolic pressure and the pulmonary capillary wedge pressure (PCWP). The increased pressure in the pulmonary capillaries and veins leads to a transudation of fluid into the interstitial tissues of the lung (interstitial edema), and later into the alveoli, producing alveolar flooding. Acute LV failure may vary in severity. When mild, it is characterized by paroxysmal attacks of breathlessness, which abate spontaneously; these attacks are related to sharp but transient rise in the LV end-diastolic and the capillary wedge pressures. When severe, it is associated with frank pulmonary edema, the patient literally drowning in his own secretions. Fulminant pulmonary edema is associated with an increase in the LV filling pressure (LV end-diastolic pressure) close to or more than 30 mm Hg.[1,2]

Acute LV failure with pulmonary edema constitutes an important cause for emergency admission to an intensive care unit (ICU). Also, patients admitted to an ICU for other critical illnesses may suddenly develop acute pulmonary edema due to LV dysfunction. The latter may be pre-existing but may have gone undetected, and could well be unmasked by the stress of a critical illness (e.g. fever, tachycardias, seizures), or by therapy used to treat a critical illness, e.g. fluid infusions, which cannot be easily handled by a diseased or poorly functioning left ventricle. LV dysfunction and failure can also be induced in a previously healthy heart by an acute illness, e.g. overwhelming sepsis, or a fulminant viral infection for which the patient has been admitted to the ICU.

HEMODYNAMIC PROFILES IN LEFT VENTRICULAR FAILURE

Failure of the pumping action of the left ventricle leads to two basic disturbances in the hemodynamics of the circulation—

1. An increase in backward pressure from the failing left ventricle, which results in pulmonary edema.
2. A failure of forward flow, which leads in time to a decreasing cardiac output, decreasing arterial blood pressure, and above all to a fall in tissue perfusion.

Both the above features may be present in varying degrees in the same individual. Also each one of these disturbances may occur independently of the other (see Chapter Cardiogenic Shock). The following hemodynamic patterns may be observed—

1. An increased LV end-diastolic pressure and PCWP with resulting pulmonary edema; an adequate forward flow with a cardiac index not less than 2.5 L/min/m^2 and adequate tissue perfusion. To start with, the cardiac output in acute LV failure may be normal in spite of pulmonary edema, because the ventricle still responds to the increase in preload, as per Starling's law—a basic compensatory mechanism in cardiac failure. The arterial pressure is unchanged and for various reasons may even show a temporary rise.

   The mechanics of this hemodynamic change is illustrated in Figure 1 which shows the right and LV function curves in a patient with acute pulmonary edema due to poor LV function. Two features worthy of note in this figure are: (i) a normal right ventricular function curve; (ii) a LV function

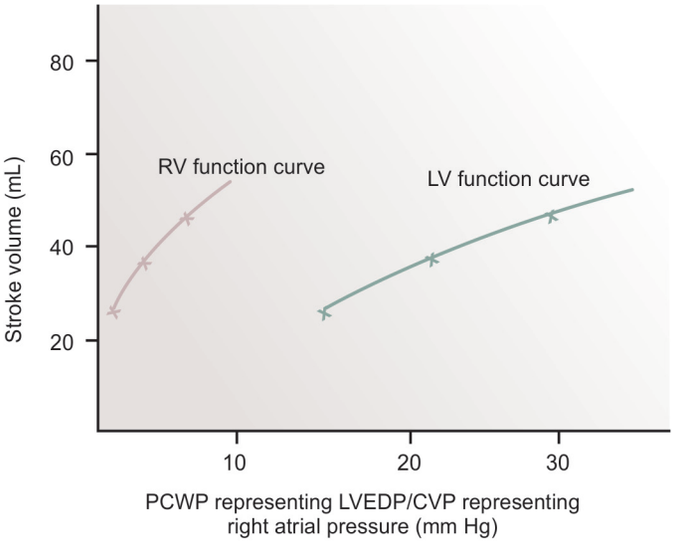

Fig. 1: Right and left ventricular (LV) function curves in a patient with acute LV failure causing fulminant pulmonary edema. Note that the LV function curve is shifted to the right, and has a lesser slope compared to the right ventricular (RV) function curve. Fulminant pulmonary edema occurs when pulmonary capillary wedge pressure (PCWP) exceeds 30 mm Hg, at which time the right atrial pressure is about 7 mm Hg. Note that a rise in right atrial pressure from 2 mm Hg to 7 mm Hg is associated with a rise in the LV filling pressure from 15 mm Hg to 32 mm Hg

curve which is shifted to the right, and whose slope is moderately reduced.

2. Increased PCWP causing pulmonary edema; a failure of forward flow with a drop in the cardiac index to less than or equal to 2.2 L/min/m^2, and a fall in tissue perfusion. As failure of forward flow increases, the arterial blood pressure drops in spite of compensatory mechanisms. The mechanics of this hemodynamic change is the same as in (1) except that the slope of the LV function curve is markedly reduced, pointing to a more severe dysfunction than in the first case (see Chapter Cardiogenic Shock).
3. No pulmonary edema as the PCWP is not raised; however, there is marked failure of forward flow with a low cardiac index (often <1.8 L/min/m^2), a low arterial blood pressure and poor tissue perfusion often causing a lactic acid acidosis. The picture is akin to that of cardiogenic shock without pulmonary edema. This hemodynamic profile has been dealt with in the Chapter Cardiogenic Shock.
4. Increased right-sided heart pressures together with the increased left-sided heart pressures noted above. Thus, in addition to an increased LV end-diastolic pressure and PCWP, there is also an increased pulmonary artery pressure, increased right ventricular end-diastolic and right atrial pressure and a rise in the central venous pressure. This is due to a progressive increase in pressure backward from the failing left ventricle, ultimately resulting in right heart failure. The clinical picture is not only that of pulmonary edema, but also includes raised jugular venous pressure, enlarged tender liver and pitting edema of the feet. This picture of congestive cardiac failure (left- and right-sided heart failure) can evolve rapidly as after a massive anterior myocardial infarct or evolves subacutely if a patient with LV failure is inadequately treated or brought late to the ICU.

SYSTOLIC AND DIASTOLIC HEART FAILURE

There are significant differences between the pathophysiology of systolic heart failure (SHF) and diastolic heart failure (DHF) even though the clinical features in both are very similar. SHF is due to diminished contractility of the myocardium. In chronic SHF, there is progressive eccentric remodeling of the left ventricle leading to progressive dilatation and a resultant decrease in left ventricular ejection fraction (LVEF). In DHF, there is concentric remodeling with a normal LV end-diastolic volume.

The hallmark of DHF is diastolic dysfunction. DHF has been defined as impaired LV filling capacity due to abnormalities in active relaxation and to increased stiffness (i.e. lowered compliance) of the myocardium. Hemodynamically these changes become evident as an upward and leftward shifted end-diastolic pressure volume relationship. In DHF, the contractility of the myocardium (in contrast to SHF) is normal so that ejection fraction is within normal limits.

Among the general heart failure population, close to half have DHF. DHF increases with age; it is present in 46% of patients more than 45 years of age and increases to near 60% in patients older than 85 years.

The important risk factors for diastolic dysfunction and DHF are hypertension, increasing age, obesity, female sex, diabetes, aortic stenosis, chronic kidney disease and coronary artery disease. Restrictive cardiomyopathy, positive pressure mechanical ventilation and pericardial effusion can also through different mechanisms impair diastolic LV filling.[3-5]

It is important to remember that in many patients systolic and diastolic dysfunction co-exist. This is typically seen in patients with coronary artery disease. Systolic dysfunction and systolic failure in these patients can be caused by new or old myocardial infarction (loss of contractile mass) and by active or acute myocardial ischemia. Diastolic dysfunction and failure can result from replacement of muscle by fibrous tissue following infarction and by the acute reduction in myocardial distensibility during ischemia.

Measurement of the PCWP does not distinguish between systolic and DHF because the wedge pressure is increased in both. However, the LV end-diastolic volume for a given end-diastolic pressure is significantly greater in systolic dysfunction when compared to diastolic dysfunction.

The diagnosis of DHF is made by the presence of clinical symptoms and signs of the LV failure in combination with preserved LV systolic function (LVEF >50%). Evidence of diastolic dysfunction is obtained by echocardiography, Doppler examination, and if the need arises by invasive hemodynamic study. The B-type natriuretic peptide (BNP)

is elevated in both systolic and DHF but values are typically lower in DHF compared to SHF.

Echocardiographic Criteria for Diagnosis of Diastolic Dysfunction

Echocardiography is a reliable noninvasive investigation to determine the presence and degree of diastolic dysfunction. Color M-mode and Doppler tissue imaging have been recently introduced for the diagnosis of diastolic dysfunction.

Mitral flow velocity determined by using pulsed wave Doppler consists of four variables: (1) peak early diastolic flow (E), (2) peak late diastolic flow (A), (3) early deceleration time (DT) and (4) A wave duration (A dur). The normal E/A ratio is 0.75–1.5 and the normal deceleration is less than 220 milliseconds.

With progressive increase in diastolic dysfunction, there is an increase in the E/A ratio to greater than 1.5 (the E wave being large and the A wave small), and a significant decrease in the DT (<150 milliseconds). If this pattern remains fixed with the Valsalva maneuver, the diastolic dysfunction is judged to be advanced or grade IV.

Precipitating factors for LV failure and pulmonary edema in patients with diastolic dysfunction include pressure overload, volume overload, rhythm disturbances causing a fast ventricular rate and myocardial ischemia. The above precipitating factors need to be controlled in management of failure.

DIAGNOSIS[1]

The diagnosis of pulmonary edema due to acute LV failure is generally easy. The patient is breathless and often orthopneic.[6] Pulmonary edema is clinically manifest by crackles, which may be restricted to only the lung bases. In severe edema, loud crackles or bubbling moist sounds are heard all over both lungs; in fulminant edema, pinkish frothy edema fluid may well out of the mouth and nose, the patient literally drowning in his own secretions. Occasionally, there are more polyphonic wheezes than crackles. In rare instances, wheezing with prolonged expiration is indistinguishable from that heard in severe bronchial asthma. If the chest is not too noisy, a diastolic gallop may be generally heard; a diastolic third heart sound signifies a LV end-diastolic pressure greater than or equal to 18 mm Hg. There is often, though not always, clinical evidence of underlying left heart disease. Hypertension, acute myocardial ischemia, myocardial infarction, aortic valve disease, mitral incompetence, acute myocarditis, supraventricular and ventricular arrhythmias, complete heart block and cardiomyopathy are important causes of acute LV failure. Acute pulmonary edema can also occur when there is a sudden, sharp rise in left atrial pressure in patients with mitral stenosis. Positive pressure ventilation, particularly when associated with high positive end-expiratory pressure (PEEP) may cause LV diastolic dysfunction and failure. High output failures are characterized by arteriovenous shunting or increased demand for oxygen by tissues. They are observed

Fig. 2: Chest X-ray reveals ill-defined fluffy opacities in both lung fields as a result of pulmonary edema

chiefly in arteriovenous fistulas, severe anemia, thyrotoxicosis and beriberi. In our experience, they more often act as aggravating or precipitating factors of heart failure in patients with underlying cardiac disease. Diagnosis of the underlying etiopathology during an attack of acute pulmonary edema may be difficult, as in severe cases heart sounds and murmurs are inaudible due to the loud bubbling moist sounds, which are heard even at some distance from the patient.

A *chest X-ray* shows clear evidence of pulmonary edema (Fig. 2). Interstitial edema is observed in mild cases; alveolar edema leads to homogeneous alveolar shadows generally spreading from the hilum to the periphery. Occasionally, one lung is considerably more involved than the other. It is important to note that there can be a short time lag between the sudden rise in LV end-diastolic pressure (and with it in the PCWP), and the clinical and radiological appearances of pulmonary edema.[7]

An *electrocardiogram (ECG)* may show evidence of ischemic heart disease or of LV hypertrophy.

An *arterial blood gas analysis* in well-marked pulmonary edema shows a low PaO_2 (as low as 30–40 mm Hg), with hypocapnia. In the moribund patient or when the use of morphine has suppressed the respiratory drive, the $PaCO_2$ rises, and some degree of respiratory acidosis results. In patients with a failing forward flow and impaired tissue perfusion, there is a super-added metabolic (lactic acid) acidosis. A combination of metabolic and respiratory acidosis is of sinister prognosis.

Echocardiography A transthoracic echocardiogram provides information related to ventricular size and systolic function, wall motion, valvular structure and function, presence of intracardiac clots or masses, intracardiac flow, pericardium and ascending and transverse aorta. A normal or near normal LVEF should never preclude the diagnosis of acute pulmonary edema, as diastolic dysfunction may occur with normal or near normal ventricular systolic function in 40% of patients with heart failure.[3-5]

DIFFERENTIAL DIAGNOSIS

When acute LV failure is associated with wheezing and prolonged expiration, it closely resembles a late-onset bronchial asthma. The diagnosis becomes doubly difficult when a patient with a past history of long-standing bronchial asthma develops LV disease. In fact, these are just the patients who when they develop acute LV failure, will manifest with wheezing rather than auscultatory crackles. We have been convinced over the years that individuals with increased bronchial reactivity wheeze rather than 'crackle' during LV failure.

Rarely, it is difficult to distinguish between pulmonary edema resulting from LV failure and noncardiogenic pulmonary edema. A careful clinical history, the evolution of the disease and relevant investigations generally clarify the diagnosis. A PCWP greater than 18 mm Hg as measured by a Swan-Ganz catheter points to LV failure. It must be remembered that a patient with LV dysfunction may well suffer from an unrelated illness that can cause noncardiogenic pulmonary edema; in such individuals more than one cause may be responsible for the pulmonary edema.

MANAGEMENT (BOX 1)[8]

The patient with acute pulmonary edema due to LV failure is nursed propped up in bed. If possible, he should be made to sit up with his legs dangling over the side of the bed. If pulmonary edema is associated with marked failure of forward flow and features of shock, he may need to be nursed flat in bed with the head slightly raised.

Morphine Sulfate[9]

This is an invaluable drug for use as the first immediate emergency measure. Morphine sulfate (15 mg) can be given subcutaneously in moderately severe LV failure. Alternatively, 2–4 mg of the drug is administered intravenously and the dose repeated after 0.5–1 hour if necessary, so that the desired effect of morphine is obtained. Morphine helps in several ways: (1) it allays anxiety, restlessness, and slows the respiratory rate, thereby reducing the work of breathing, and also the overall oxygen demand by the peripheral tissues (through sedation and quietening of the patient); (2) it dilates both arterioles and venules thereby increasing venous capacitance and reducing the preload. A reduced preload causes a drop in the PCWP and in the filling pressure of the left ventricle. This results in a reduction of pulmonary edema.

Morphine is at times impossible to obtain in hospitals and ICUs in India. A useful substitute (but not an equally effective one) is buprenorphine given slowly intravenously in a 0.2–0.4 mg dose. This may need to be repeated till the desired effect is achieved.

Pethidine 75–100 mg intramuscularly can also be used, but lacks the overall efficacy of morphine. The only situation where pethidine is preferable is in patients in acute LV failure who present with severe wheeze and prolonged expiration.

Box 1: Management of acute pulmonary edema due to left ventricular failure

- Morphine 2–4 mg intravenously (IV), or buprenorphine 0.2–0.4 mg IV, repeated after 0.5–1 hour if necessary. If morphine is not available, pethidine 75–100 mg intramuscularly (IM) can be used. Patients with fulminant pulmonary edema and alveolar hypoventilation should first be put on mechanical ventilator support and then administered morphine
- Oxygen at 6–8 L/min through nasal prongs
- Measures to reduce preload—
  - Furosemide 40–100 mg IV
  - Aminophylline 250 mg diluted with dextrose and given IV over 10–15 minutes
  - Application of rotating tourniquets or blood pressure (BP) cuffs to extremities may be used during transport to hospital
- Digitalis—improves cardiac contractility and pump function 0.25 mg given IV slowly and repeated 4–6 hourly till digitalizing dose of 0.75–1 mg given in 24 hours
- Vasodilators—
  - IV nitroglycerine in a slow titrated drip starting at 15 µg/min—reduces preload
  - IV sodium nitroprusside in a slow titrated drip starting at 5 µg/min—reduces both preload and afterload
- Inotropic agents (dopamine/dobutamine) used—
  - When pulmonary edema associated with hypotension and/or reduced tissue perfusion
  - In patients with pulmonary edema refractory to the above-mentioned treatment
- Ventilator support—
  - In fulminant pulmonary edema
  - When respiratory drive fails and patient breathes poorly
  - Respiratory muscle fatigue

Note: Nitroprusside is best avoided except when LV failure is associated with severe hypertension.

In a few of these patients, morphine instead of relieving the wheeze actually worsens it. The major side effects of morphine include hypotension, vomiting, and increased parasympathomimetic activity evinced by bradycardia and bronchospasm. Some patients with acute LV failure may show a strong hypertensive response during the period of failure, even though they are not basically hypertensive. Morphine acts beautifully in such patients and lowers the blood pressure effectively. Vomiting can be controlled by the use of promethazine 25 mg intramuscularly. Most patients with acute LV failure and pulmonary edema have tachycardia, so that a lowering of the heart rate by morphine is a decided advantage. If parasympathomimetic effects are observed, the administration of atropine 0.5 mg intravenously easily reverses these effects.

There is just one strong contraindication to the use of intravenous morphine in patients with acute LV failure. It should not be used as an immediate measure in a patient with fulminant pulmonary edema who is literally frothing with

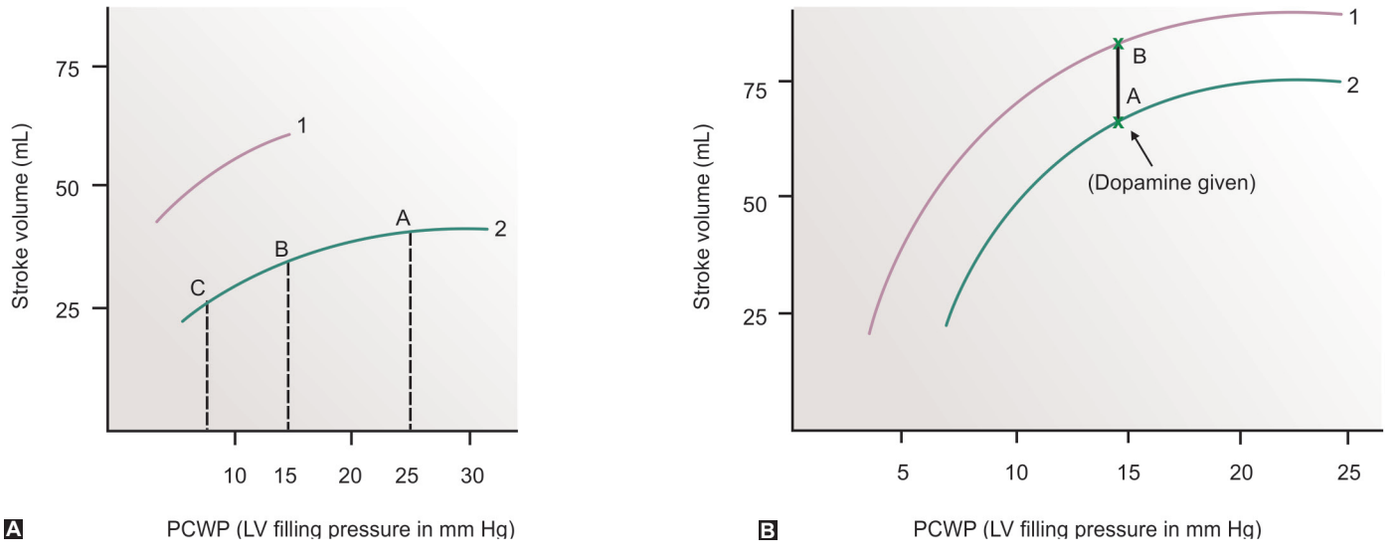

Fig. 3A and B: (A) 1-Normal left ventricular (LV) function curve; 2-LV function curve in patient with LV dysfunction. Administration of furosemide (Point A) reduces preload, causes a fall in pulmonary capillary wedge pressure (PCWP) (Point B), and relieves pulmonary edema, but does not influence stroke volume or cardiac output. Over-use of furosemide will further reduce pulmonary capillary wedge pressure (PCWP) (to Point C) and though pulmonary edema is further relieved, there is now a fall in the already low cardiac output. (B) LV function curves (1) before administration of dopamine; (2) after dopamine administration. In contrast to (A) the use of dopamine improves the cardiac contractility to almost normal levels (point A to point B)

edema fluid. Such patients have ineffective breathing and in fact, their blood gases always show a raised $PaCO_2$ pointing to alveolar hypoventilation. A few of these patients are also so severely hypoxic, that they are obtunded. The use of morphine as the first measure in these patients invariably produces a respiratory arrest. As will be discussed below, these patients should be promptly intubated and ventilated; morphine should be given only subsequent to this emergency procedure.

Oxygen

This is promptly started to combat hypoxia, either through a nasal catheter or nasal prongs at 6–8 L/minute, or through a well-fitting oronasal mask at 5–6 L/minute. In patients with well-marked pulmonary edema, oxygen can be given under continuous positive pressure using a well-fitting oronasal mask. This may provide satisfactory oxygenation, and may at times prevent the need for emergency intubation and ventilatory support.

Measures to Reduce Preload

Use of Diuretics—Furosemide[10-12]

Intravenous furosemide is useful in the management of acute pulmonary edema. Between 40 mg and 100 mg or even more of the drug is given intravenously, depending on the severity of pulmonary edema. Furosemide reduces preload in two ways—

1. It produces almost within minutes a sharp increase in venous capacitance through a venodilating effect, which results in a significant lowering of the preload (as measured by the pulmonary artery end-diastolic and PCWPs). Pulmonary congestion thereby decreases even before the onset of the diuretic action of the drug. There is at times a fall of 5–8 mm Hg in the LV filling pressures after intravenous furosemide.
2. It has an excellent diuretic action. Diuresis starts within 15 minutes and is maximal for 4–6 hours. Some patients are exquisitely sensitive to even small doses (40 mg) of furosemide, and respond with profuse diuresis. Therefore, unless the pulmonary edema is gross, it is wiser to give only 40 mg furosemide initially and then repeat a larger dose if diuresis is inadequate in the first 2 hours. At times, patients require massive doses of furosemide (1 g over 24 hours) to promote an effective diuresis. When more than 100–120 mg of intravenous furosemide are required to produce an effective diuretic effect, it is best to administer the drug by a continuous IV infusion at a rate of 10–40 mg/hour.

The diuresis induced by furosemide reduces the water content of the lungs and thus reduces pulmonary edema. It is important to note that diuretics do not significantly increase cardiac output. In fact, over-diuresis with an over-reduction in the preload is a disadvantage, as this may initially cause a fall in the cardiac output. It is currently believed that a fall in the cardiac output may be further contributed to by an increase in systemic vascular resistance. The latter effect is due to a furosemide-induced stimulation of release of renin and raised circulating angiotensin levels.[13] Figure 3A illustrates the effect of furosemide on the LV function curve in left heart failure. In contrast, the administration of dopamine to these patients improves the cardiac contractility to almost normal levels (Fig. 3B).

The danger of overuse of furosemide is twofold—it renders the patient hypovolemic and can reduce the cardiac output, the sum total of these effects being an impairment of tissue perfusion. The above problems may prove dangerous if

the kidneys continue to be whipped by increasing doses of furosemide, in an attempt to increase a falling urine output in a hypovolemic patient. Features of hypovolemic shock (which may include oliguria and even renal shutdown), may thus be wrongly attributed to cardiogenic shock produced by poor pump function.

Use of Vasodilators

Vasodilators are important in the management of cardiogenic pulmonary edema. Nitrates chiefly act by reducing the preload, whilst sodium nitroprusside when used in selected cases acts by reducing both the preload and the afterload.

Nitrates[14,15] A slow drip of intravenous nitroglycerine is always used in patients with well-marked cardiogenic pulmonary edema, starting with 15 µg/minute and progressively increasing the concentration till the desired relief is obtained. The blood pressure is carefully monitored, and as described under the management of cardiogenic shock, should not be allowed to fall below 100 mm Hg systolic. In previously hypertensive patients, the systolic blood pressure should not be allowed to fall below 130–140 mm Hg. The other side-effects of intravenous nitroglycerine have been discussed at length under cardiogenic shock. It is not always necessary to use a Swan-Ganz catheter for monitoring the PCWP when using intravenous nitroglycerine; noninvasive monitoring with careful clinical assessment generally suffices. However, invasive hemodynamic monitoring is resorted to, when pulmonary edema is associated with poor forward flow and impaired tissue perfusion.

In less severe cases of cardiogenic pulmonary edema, the use of isosorbide dinitrate 10 mg 4 hourly suffices. One can use the drug either sublingually or orally with a careful watch on the arterial blood pressure.

The liberal use of a trinitrate ointment (2–2.5" patch) applied on the skin is also helpful in reducing preload. This method can be used after the patient has been weaned off the intravenous nitroglycerine infusion, which may take from 1 day to 4 days. The trinitrate ointment can be applied on the skin concurrently with oral isosorbide therapy. The ointment can be promptly rubbed off if the arterial blood pressure starts to drop.

Sodium nitroprusside[16] It may be used as a slowly titrated intravenous drip (starting at 5 µg/minute). It reduces both arteriolar and venous resistance thereby reducing both afterload and preload. Reduction of preload relieves pulmonary congestion and edema; reduction of afterload improves the pumping action of the heart.

- Sodium nitroprusside is particularly useful in patients who have pulmonary edema due to LV failure and who also have well-marked hypertension. If used, there should be facilities to monitor the pulmonary artery pressure though a Swan-Ganz catheter and the systemic arterial pressure through an intra-arterial catheter. The use of intravenous nitroprusside in the absence of these monitoring facilities can be tricky and dangerous, particularly in the hands of the inexperienced. The drug should not be used in patients with acute LV failure and pulmonary edema, who are also in cardiogenic shock.

The side effects of nitroprusside, particularly a precipitous fall in blood pressure, should be carefully monitored.

Aminophylline

Aminophylline (0.5 g in a slow intravenous infusion) is administered only in the presence of severe bronchospasm. Aminophylline however, also has a venodilating effect, thereby reducing venous return and preload.

Use of Digitalis[17-19]

Digitalis improves cardiac contractility and therefore improves pump function in LV failure. For prompt effect, digoxin is given in a dose of 0.25 mg very slowly, intravenously. This is repeated every 4–6 hourly till a total digitalizing dose of 0.75–1 mg is given over 24 hours. If the patient has already been taking adequate doses of oral digitalis prior to the onset of acute LV failure with pulmonary edema, it is best to avoid intravenous use of the drug. However, if it is given, no more than 0.125 mg is administered. Determination of serum digoxin levels helps in titrating the dose of digitalis. In a patient who has already been receiving digitalis, the presence of paroxysmal atrial tachycardia with a 2:1 block, A-V junctional tachycardia or recurrent ventricular bigeminy are all suggestive of digitalis toxicity.

Inotropic Agents[20]

An intravenous infusion of dopamine or dobutamine is used under the following conditions in patients with cardiogenic pulmonary edema (Fig. 3B). Their dosage and manner of use have been described on the Chapter Cardiogenic Shock.

- When acute pulmonary edema is associated with hypotension and/or evidence of impaired tissue perfusion.
- When pulmonary edema does not relent quickly in spite of the measures outlined above.

Dobutamine is preferred unless the systolic blood pressure is l below 90 mm Hg, in which case dopamine is used.

Recognition of Factors Frequently Precipitating LV Failure and Pulmonary Edema in the ICU (Box 2)

Important precipitating factors causing cardiogenic pulmonary edema in patients being treated for some other critical illness in the ICU include—

- Increased salt intake.
- *Overloading patients with fluids through intravenous infusions* Pulmonary edema may be triggered in patients with underlying poor LV function by the rapid infusion of fluids, even if the fluid intake is by no means excessive. This is particularly common when intravenous infusions of whole blood, plasma or colloid are given rapidly to patients with poor LV function.

Box 2: Important factors precipitating left ventricular failure (LV) and pulmonary edema in critically ill patients in the intensive care unit (ICU)

- Increased salt intake
- Overloading patients with fluids through intravenous infusions. In patients with LV dysfunction, rapid infusion of fluids (particularly whole blood, plasma, colloids, even if not excessive) may trigger pulmonary edema
- Occurrence of tachyrhythms, e.g. supraventricular tachycardia, atrial fibrillation with fast ventricular rate or ventricular tachycardia. In critically ill patients, even sinus tachycardia due to fever, seizures can increase the workload of the heart and precipitate pulmonary edema
- Occurrence of marked bradyrhythm can increase the filling pressures and precipitate pulmonary edema

- *The occurrence of tachyrhythms* Sinus tachycardia produced by fever, marked restlessness, involuntary movements or seizures, increases the workload on the heart in critically ill patients, and triggers cardiogenic pulmonary edema, thereby unmasking LV failure in these patients. Supraventricular tachycardias, atrial fibrillation with a fast ventricular rate or ventricular tachycardias can have an even more disastrous effect in critically ill patients.
- A marked bradyrhythm can also result in increased filling pressures and cardiogenic pulmonary edema. Pacing may be required to increase the heart rate and reverse the pulmonary edema, particularly if intravenous atropine proves ineffective.
- Severe anemia, thyrotoxicosis and vitamin B_1 deficiency may act as precipitating or contributory factors in acute heart failure.

Acute LV Failure Presenting with Severe Bronchospasm (True Cardiac Asthma)

Patients with a background of asthma or hyperreactive bronchi often present with severe bronchospasm when they develop acute LV failure due to underlying LV disease. In addition to the treatment outlined above, administration of methyl prednisolone 20–40 mg 8 hourly intravenously and nebulization with salbutamol are helpful. Aminophylline 0.5 g administered in an intravenous infusion over 24 hours is also of use.

Use of Ventilator Support in Cardiogenic Pulmonary Edema

This is indicated in the following conditions—

- *Fulminant pulmonary edema* in which secretions bubble within the trachea and the larger bronchi. The patient is grossly hypoxic, often cyanosed, with a PaO_2 less than 45 mm Hg, and often as low as 30 mm Hg. These patients almost always hypoventilate because of ineffective respiration, and this is evinced by a $PaCO_2$ greater than 50 mm Hg. Prompt endotracheal intubation and the use of volume cycled ventilation with inspired oxygen (FiO_2) at 100% is life-saving. Oxygenation improves, ventilation is satisfactory and the positive pressure forces the edema fluid back against the alveolar walls, and at least prevents further transudation of fluid. A PEEP of +5 to +10 cm of water is of help. The therapy described above is often life-saving in a patient with fulminant pulmonary edema who has a palpable pulse and a satisfactory arterial blood pressure (>90 mm Hg). It buys valuable time and gives other therapeutic measures, particularly the use of morphine, digoxin, furosemide, intravenous nitroglycerine infusion and intravenous dopamine support, a chance to take effect. If, however, ventilator support is delayed to a point in time when the pulse is barely perceptible and the arterial blood pressure unrecordable, the prognosis is poor. *In less fulminant cases, noninvasive ventilator support through an orofacial mask is equally effective.*
- *When the respiratory drive fails*, and the patient is observed to breath poorly. This occurs terminally in severe pulmonary edema, or is the result of respiratory muscle weakness in critically ill patients. It also occurs when the respiratory drive has been excessively depressed by the use of morphine or pethidine. A poor respiratory drive is noted clinically and confirmed by blood gas analysis, which shows increasing hypoxia and a rise in $PaCO_2$. The average patient with cardiogenic pulmonary edema is hypocapnic; hence increasing hypercapnia with a $PaCO_2$ of greater than 60–70 mm Hg can portend disaster.

Mechanical Support

In patients with pulmonary edema and severe shock unresponsive to conventional methods, mechanical support with an intra-aortic balloon pump or rarely with a ventricular assist device may help to temporarily tide over a crisis.

Invasive Monitoring in Cardiogenic Pulmonary Edema

Clinical judgment with routine noninvasive tests (which should include chest X-ray and arterial blood gas analysis) generally suffice to guide management. A Swan-Ganz catheter with monitoring of pulmonary artery and PCWPs (and indirectly of LV filling pressures), and measurement of cardiac output are indicated under the following circumstances—

- When the diagnosis of cardiogenic versus noncardiogenic pulmonary edema is uncertain on clinical grounds.
- When the knowledge of a patient's volume status is of vital importance, but cannot be determined from the history and clinical examination.
- In severe cases of pulmonary edema which do not respond to conventional therapy.
- On rare occasions when intravenous sodium nitroprusside is used to reduce both afterload and preload.
- When acute pulmonary edema is associated with a sharp fall in arterial blood pressure, reduced tissue perfusion or with obvious shock.

- When in a patient presenting as acute heart failure, it is important to exclude cardiac tamponade or an acute left to right shunt.

Improvement in cardiogenic pulmonary edema is gauged clinically and by chest X-rays. In patients with a Swan-Ganz catheter, one can titrate therapy to maintain the PCWP close to 15–18 mm Hg, ensuring that a fall in preload does not cause a sharp fall in the cardiac index. It is important to remember that there is a significant time lag between reduction of preload with a fall in the PCWP to safe levels and the radiological clearing of edema fluid. It is therefore important not to overdiurese these patients merely because of persistent alveolar shadows in the lung fields, as this could lead to unwanted hypovolemia.

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CHAPTER 23

Tachyarrhythmias in the Intensive Care Unit

Tachyrhythms occur very frequently in patients under intensive care. They are not restricted to patients with underlying heart disease; in fact, they occur against a wide spectrum of background diseases—in shock from any cause, acute infections, acute respiratory problems, during ventilator support, following hypoxia, and fluid and electrolyte disturbances. The sudden appearance of a tachyrhythm in a critically ill patient or in a patient on his way to recovery from a critical illness invariably makes even an experienced critical care physician's heart skip a beat! What is it due to? Should one react to it and if so how? Some tachyrhythms come and go all in a flash and produce no problems; others portend disaster. The answer to the two questions listed above, in spite of experience and wisdom gathered over the years, can sometimes be unfortunately given only by hindsight rather than by foresight.

Tachyrhythms can result from enhanced automaticity, triggered activity as in ectopic impulses or from a process called *re-entry*. In the *re-entry phenomenon*, a triggered impulse encounters a block when being propagated forwards through a conducting pathway. The impulse, however, is permitted to pass in the return or retrograde direction. Retrograde transmission can allow such a triggered impulse to result in a continuous self-sustained tachycardia. The re-entry phenomenon is an important underlying mechanism in many paroxysmal tachycardias.

This chapter has not dealt in detail with the electrophysiology and detailed mechanisms underlying tachyrhythms. It briefly deals with the quick recognition of the nature of different tachyrhythms, and describes the urgent management strategies in an identified tachyrhythm occurring in an intensive care unit setting. This is followed by a brief section on digitalis-induced arrhythmias. The next chapter details relevant aspects of important and commonly used drugs in the management of tachyarrhythmias.

QUICK RECOGNITION OF TACHYRHYTHMS

A quick study of the rhythm strip is of great help in identifying the nature of the tachyarrhythmia. The features that should be quickly noted are the rate, the regularity or irregularity of the RR intervals, and the width of the QRS complex—whether less than 0.12 seconds, equal to or greater than 0.12 seconds.

Narrow complex (QRS <0.12 s) regular tachycardias[1] are sinus tachycardia, atrial flutter with a fixed block, paroxysmal atrial tachycardia, junctional (nodal) tachycardia or atrioventricular (AV) nodal re-entrant tachycardia. A look at the P-waves in a rhythm strip can help in further identification. Uniform P-waves suggest a sinus tachycardia, saw-tooth P-waves an atrial flutter, inverted P-waves a junctional (nodal) tachycardia, absent P-wave activity a paroxysmal atrial tachycardia, multiple varying P-waves a multifocal atrial tachycardia. It is preferable to monitor V_1 so that the rhythm strip will depict a V_1 tracing where the P-wave configuration, particularly in atrial flutter, is quickly discernible. A 12-lead tracing to study P-waves and their configuration is however often necessary.

Marked irregularity of a narrow complex tachycardia is observed in atrial fibrillation, multifocal atrial tachycardia, atrial flutter with varying block and when there are many supraventricular ectopic beats in patients with sinus rhythm.

The rate as computed from a rhythm strip is of comparatively less value. It, of course, distinguishes a tachyrhythm (>100 beats per minute) from a bradyrhythm (<60 beats per minute). Sinus tachycardia is uncommon with rates greater than 200 beats per minute. Again, the higher the rate in a

tachyrhythm, the greater is the chance of a compromised circulatory system.

Wide complex (QRS >0.12 s) tachycardias[2] can be ventricular tachycardia (VT), supraventricular tachycardia (SVT) with delayed or aberrant conduction, or torsade de pointes which is a particularly dangerous form of VT. To distinguish between VT and SVT with delayed or aberrant conduction can be extremely difficult. Relevant distinguishing features are discussed later. As a matter of principle, a wide QRS tachyarrhythmia should be considered to be a VT unless clearly proved otherwise.

A short description of narrow QRS complex tachycardias and management strategies to counter them is now given. This is followed by a similar description of wide QRS tachyrhythms.

NARROW COMPLEX TACHYCARDIAS (SUPRAVENTRICULAR TACHYCARDIAS)

General Considerations

Patients in the ICU with narrow complex or SVTs often have underlying cardiac disease involving the conduction pathways. However, supraventricular arrhythmias can also occur in the absence of organic heart disease. They can thus be caused by hypokalemia, hypomagnesemia, hypoxia, increased adrenergic activity or tone, or by drugs. Most paroxysmal supraventricular tachyrhythms are caused by re-entry mechanisms. Re-entrant tachycardia is initiated by a supra-ventricular ectopic beat and is promptly terminated by a direct current (DC) shock or by overdrive pacing. Occasionally, SVTs are caused by a sudden enhancement of an autonomous focus in the atria or the junctional AV nodal tissue, which discharges or fires at a rate generally between 150–220 beats per minute. Enhanced autonomic activity of an ectopic focus is often due to metabolic derangements or to drugs, and SVTs due to this etiology often respond to a correction of the underlying metabolic derangement. Though all SVTs are sudden in onset and offset, SVT due to enhanced autonomic activity are not as sudden as those due to re-entry mechanisms.

ATRIAL FLUTTER AND FIBRILLATION

Atrial flutter is characterized by typical flutter waves (described later) at a rate of 300–350 beats per minute. A block at the AV node, generally a 2:1 block allows the ventricles to beat regularly at 150 beats per minute. A varying AV block produces an irregular ventricular rhythm.

Atrial fibrillation[3] is the most common supraventricular arrhythmia. The atria fibrillate and the ventricular rhythm is irregularly irregular because of a constantly changing AV block. Atrial fibrillation is usually associated with cardiac disease—chiefly hypertension, ischemic heart disease, mitral valve disease and congestive heart failure. In about one-third of patients, it occurs without clinical evidence of cardiac disease—lone atrial fibrillation.

As mentioned briefly earlier, identification of the atrial activity (P-waves) and its form is of crucial importance. It helps, as will be discussed later, to distinguish between SVT with delayed conduction and VT, and also helps to arrive at the nature of a SVT with narrow QRS complexes. A full 12-lead electrocardiogram (ECG) aided by carotid sinus massage (a vagal maneuver that slows the heart, and thereby brings out the P-wave) may be necessary. If no emergency exists, the use of an esophageal lead will invariably identify atrial activity.

Clinical Presentation[3]

The main presentation of most supraventricular tachyarrhythmias is the sudden onset of regular palpitations with an abrupt onset. This is particularly so with AV nodal re-entry tachycardia and AV re-entry tachycardia. Tachycardia, which involves the re-entry phenomenon through the AV node, can often be terminated by the Valsalva maneuver. Other symptoms include dizziness, weakness, diaphoresis, chest discomfort and polyuria due to the release of atrial natriuretic peptide.

Syncope may occur in 10–15% of patients, particularly if the ventricular rate is over 200 beats per minute. It is observed more commonly if the patient remains standing, occurs generally at the onset of the arrhythmia or occurs following a long pause after the termination of the arrhythmia. In older patients with a background heart disease, such as mitral valve stenosis, aortic stenosis, ischemic heart disease, poor left ventricular function, hypertrophic obstructive cardiomyopathy, or in patients with cerebrovascular disease, even a moderately fast ventricular rate can cause hemodynamic collapse with profound hypotension and syncope.

A point of importance is that patients presenting with AV re-entry tachycardia may also present with atrial fibrillation. If an accessory pathway has a short antegrade conduction, it may conduct to the ventricles at a very high rate and cause ventricular fibrillation (VF) and death. Sudden death from supraventricular tachyarrhythmia in otherwise young healthy individuals though rare may well be related to this phenomenon.

Irregular palpitations are observed in atrial fibrillation, atrial flutter with changing block, multifocal atrial tachycardia and multiple atrial premature beats. In patients with poor ventricular function, uncontrolled atrial fibrillation, can cause rapidly progressive congestive heart failure, hypotension and hemodynamic collapse. Atrial fibrillation with very slow AV conduction or complete heart block (Frederick's syndrome) can also cause hemodynamic collapse.

SINUS TACHYCARDIA

This is the commonest tachycardia seen in the ICU. Though the rate is generally below 200 beats per minute, in young patients with acute infections (and in severe tetanus in particular), the rate may exceed 200 beats per minute. The P-wave has a normal configuration. Sinus node re-entry tachycardias and atrial tachycardia due to autonomic activity from an

ectopic focus close to the SA node may be indistinguishable from sinus tachycardia. Tachycardias decrease diastolic filling time; in a normal heart, the heart rate must exceed 180 beats per minute before the cardiac output falls.[3] In poorly compliant ventricles, diastolic filling and cardiac output are reduced with comparatively smaller increases in the heart rate. The management of sinus tachycardia is to first identify and then treat its cause. An unexplained rise in an otherwise stable pulse rate in a critically ill individual is a matter of common concern. Important causes of sinus tachycardia are severe anxiety, unrelieved pain, hypovolemia, hypoxemia, sepsis, infection, early shock from any cause, blood loss, pneumothorax, pulmonary embolism, the use of adrenergic drugs, myocardial ischemia or infarction and thyrotoxicosis. Once the cause is treated, the sinus tachycardia disappears. Sinus tachycardia in patients with myocardial ischemia or infarction may warrant the use of beta blockers to slow the heart rate and thereby reduce the oxygen demands of the myocardium. Beta blockers should however not be used in patients with ischemic heart disease who also have poor pump function see Chapters Unstable Angina and Acute Myocardial Infarction).

ATRIOVENTRICULAR NODAL RE-ENTRY TACHYCARDIA[4]

An AV nodal re-entry tachycardia involves dual anatomical and functional pathways in the AV node. One pathway has a long refractory period and faster conduction; the other has a short refractory period and slower conduction. Normally, the impulse arising from the SA node passes through the fast pathway to depolarize the ventricles. If an atrial ectopic beat occurs early when the fast pathway is refractory, the impulse is blocked so that it is now propagated to the ventricle through the slower pathway. It then travels back via the fast pathway which by then has recovered its excitability, thereby initiating a slow-fast AV nodal re-entry tachycardia.

Electrocardiogram

The rhythm is regular at a rate of 140–250 beats per minute. The atria are activated retrogradely producing inverted P-waves in leads II, III, and aVF. However, since the atria and ventricles are depolarized simultaneously, the P-waves are buried in the QRS complexes and cannot be discerned on the ECG. In a small proportion of patients with this tachycardia, the retrograde activation of the atria is observed in the form of small positive terminal deflections in aVR or V_1, and by a small negative 's' in the inferior leads (II, III and aVF).

ATRIOVENTRICULAR RE-ENTRY TACHYCARDIA

Atrioventricular re-entry tachycardia is dependent on the presence of one or more accessory pathways connecting the atria to the ventricle. Accessory pathways capable of antegrade conduction are termed manifest. A sinus impulse conducted antegradely through an accessory pathway produces a delta wave, as it does not encounter AV delay. The PR interval is short; the QRS is wide. This occurs because the atrial impulse entering via the accessory pathway excites initially a nonspecialized part of the ventricular myocardium; depolarization proceeds slowly at first giving rise to the delta wave, before it is overtaken by depolarization occurring through the normal conducting pathways. An accessory pathway capable of conducting solely in a retrograde fashion is regarded as concealed, as it does not produce a delta wave nor a short PR interval during sinus rhythm.

Usually, the re-entry circuit in atrioventricular re-entry tachycardia consists of the impulse traveling from the atria to the ventricle through the AV node and then traveling retrogradely through the accessory pathway to reach the atrium. A circle of activation is thereby perpetuated. Rarely the atrial impulse could travel antegradely through the accessory pathway to the ventricles and return to the atria by passing retrogradely via the AV node. Atrial fibrillation is generally encountered in patients with an antegrade conducting accessory pathway.

EMERGENCY MANAGEMENT

It may be difficult in an emergency to distinguish between AV nodal re-entry tachycardia and AV re-entry tachycardia. This is not of consequence because treatment is the same for both. If the patient is hemodynamically stable, these tachycardias often respond to vagal measures, such as the Valsalva maneuver, carotid sinus massage, inducing vomiting by tickling the pharynx, or by facial immersion in cold water (diving reflex). It is important never to massage both carotid sinuses at the same time as this can result in catastrophic cardiac arrest.

Drugs that block the AV node, such as adenosine, verapamil, diltiazem and beta blockers, can terminate both AV nodal re-entry and AV re-entry tachycardias. Adenosine is the drug of choice as it terminates these re-entry tachycardias in more than 90% of cases and is effective within 30 seconds of its intravenous injection. An added advantage (when compared to verapamil or diltiazem) is the absence of a negative inotropic effect so that the drug is safe in patients who are hypotensive or have poor left ventricular function.

It is important to note that adenosine generally does not abolish atrial flutter, nor does it revert automatic atrial tachycardia. It can however produce high-grade AV block during which the atrial tachycardia persists, though the ventricular rate is slower. Adenosine has no effect on VTs.

Adenosine is administered intravenously as a very rapid 3–6 mg bolus. The bolus dose should be promptly followed by a 20 mL saline flush so as to hasten its effect. If the drug is ineffective, another 6 mg or even 12 mg is administered intravenously after 2–5 minutes, followed by 20 mL saline flush. The dose of adenosine should be reduced by 50%, if it is given through a central venous catheter instead of a peripheral vein.[5] This is because ventricular asystole is known to occur

when a standard dose of adenosine is given through a central venous catheter.

Adverse effects of adenosine include facial flushing, chest tightness, dyspnea and a bradyrhythm because of AV block. These adverse effects are short-lived as the drug is metabolized very quickly, its half-life being just 10 seconds.

Rarely, adenosine may shorten the atrial refractory period and promote atrial flutter or fibrillation or accelerate conduction over the accessory AV pathway producing a rapid ventricular response.[6] Adenosine has an important drug interaction with the bronchodilator, theophylline. Theophylline blocks adenosine receptors, thereby preventing the proper action of adenosine so that the drug may be ineffective in these circumstances. Finally, a significant side effect in asthmatic patients is bronchoconstriction. The drug should therefore not be used in patients with asthma.

Verapamil and Diltiazem

Verapamil is administered as a 5 mg IV bolus over 2 minutes; the tachycardia is expected to revert in 5–10 minutes after the injection. If necessary, a second IV bolus of 5–10 mg may be given 30 minutes after the initial dose. Its disadvantage is that it has a negative inotropic effect; also, it is not as quick and as effective in its action as adenosine. There are four contraindications to the use of verapamil—

1. It should not be used in patients with heart failure or poor left ventricular function.
2. It should not be used for broad complex tachycardias.
3. It is contraindicated if oral or IV beta blockers have already been given.
4. It should not be used in patients with atrial fibrillation associated pre-excitation syndrome, as it could result in accelerated induction over the accessory pathway, resulting in a very rapid ventricular response or even in VF.

Diltiazem

Diltiazem could be used in place of verapamil. Its negative inotropic effect is less marked, but it has a lower effective rate for termination of tachycardias compared to verapamil. The drug has the same contraindications as verapamil. The drug is administered in a dose of 0.25 mg/kg over 2 minutes. If there is no response, an additional 0.35 mg/kg is given after 15–30 minutes followed by a 5–15 mg/hour infusion for rate control.

Beta Blockers

Esmolol is the quickest acting beta blocker and allows rapid dose titration to desired effect. The dose is 500 µg/kg IV over 1 minute. It is then infused at a rate of 50 µg/kg per minute. The rate is increased by 25 µg every 5 minutes, if necessary, to a maximum of 200 µg/kg per minute. The side effects are hypotension, bradycardia and even heart block. There could be deterioration of ventricular function in patients with organic heart disease.

Metoprolol is a more readily available beta blocker. It is given in an intravenous dose of 5 mg over 2 minutes. Repeat doses of 5 mg may be given if necessary every 10–15 minutes till a maximum dose of 15 mg.

It is important to note that excessive bradycardia caused by the AV node blocking agents should be countered by the use of 0.6 mg IV atropine. This can be repeated if necessary.

The above mentioned drugs are highly effective in terminating AV nodal re-entry and AV re-entry tachycardia. If for some reason, drugs are either contraindicated or ineffective, one could try amiodarone as a 300 mg IV infusion over 30 minutes (in a 60 kg individual) followed by a 24-hour IV infusion (700–800 mg).

Digoxin (at one time in use) is now no longer used. It is poorly effective and may facilitate conduction over an accessory pathway and promote atrial fibrillation.

Atrial Pacing

In patients with implantable devices, overdrive-pacing facilities can be used to terminate the arrhythmia. However, there is also a risk of inducing atrial fibrillation with a rapid ventricular response in a patient with an antegradely conducting accessory pathway.

Long-term Management

Atrioventricular nodal re-entry tachycardia and AV re-entry tachycardia should be referred to a cardiologist for electrophysiologic evaluation and non-pharmacological alternatives, including ablation of an accessory pathway, which is widely available.

ATRIAL FLUTTER

This is a common tachyrhythm in the ICU particularly in patients with severe chronic airways obstruction and ischemic heart disease. It is also an important problem following major surgery, particularly coronary artery bypass surgery.

Mechanism

The classification of atrial flutter is dependent on the underlying electrophysiological mechanism and ECG presentation. The reader is referred to a textbook on cardiology for the different atrial flutter circuits and their electrophysiological mechanisms.

Typical, or isthmus-dependent atrial flutter involves a macroreentrant right atrial circuit, the wave front descending along the right atrial wall, between the tricuspid annulus and the inferior vena cava, and then ascending up the interatrial septum, giving rise to the most frequent pattern, named *counterclockwise flutter*. When re-entry can also occur in the opposite direction, it is termed clockwise or reverse flutter.

Electrocardiographic Presentations

The flutter waves beat at 250–350 beats per minute leading to a AV block of 2:1 or occasionally 4:1. A changing or varying block leads to an irregular ventricular rhythm. A 2:1 AV block generally causes a regular ventricular rhythm at 150 beats

per minute. Any regular fixed ventricular rate of 150 beats per minute should arouse prompt suspicion of an underlying atrial flutter, even if the flutter waves are not clearly discernible. In the most frequently observed counter clockwise atrial flutter, the typical saw-tooth flutter F-waves are negative in lead II, II, aVF and V_5, V_6 and positive in leads V_1 and V_2. Clockwise atrial flutter has positive F-waves in lead II, III, aVF and negative waves in V_1 and V_2.

Atrial flutter associated with a very fast ventricular rate as in a 1:1 conduction can produce serious hemodynamic instability and even collapse, particularly in patients with underlying organic heart disease.

ATRIAL FIBRILLATION[3]

Atrial fibrillation is characterized by rapid fibrillatory F-waves that vary in size and configuration. The response depends on the rate and irregularity of atrial activity, the refractory properties of the AV node and the prevailing sympathetic and parasympathetic tone. Many atrial impulses are blocked at the AV node, but the ventricular responses are irregularly irregular unless there is a complete AV block.

Adverse Effects of Atrial Fibrillation

The loss of effective atrial contraction in atrial fibrillation together with the decrease in diastolic filling time of the ventricles due to a fast and irregularly irregular ventricular rate impairs cardiac filling. The normal atrial kick (contraction) is responsible for 25% of the end-diastolic ventricular volume (preload). When this is lost as in atrial fibrillation, cardiac performance is hampered, particularly in patients with a noncompliant left ventricle as also in patients with ventricular systolic dysfunction. Left atrial pressures rise, followed by a rise of pressure in the pulmonary circuit causing pulmonary edema. Right-sided pressures also rise causing engorged neck veins, enlarged tender liver and pitting edema of the feet.

The other important adverse consequence of atrial fibrillation (and also of atrial flutter though perhaps to a lesser extent) is the danger of the formation of mural thrombi in the atria. This could lead to either systemic embolization (if the mural clot is in the left atrium) or pulmonary embolism (if the mural thrombus is in the right atrium).

Clinical Classification

Clinical classification of atrial fibrillation is as under—

1. First detected, paroxysmal (up to 7 days).
2. Persistent (more than 7 days).
3. Long standing persistent (>1 year).
4. Permanent.

It is important to bear this classification in mind as it helps decide between rhythm restoration and rate control. First onset atrial fibrillation (<48 hours onset) is best treated by restoration to sinus control. However, episodes of atrial fibrillation may be asymptomatic so that the first episode detected by the physician need not necessarily be the actual first. Perhaps, it would be safer to opt for rate control and anticoagulation when doubt exists on this score.

Persistent or permanent atrial fibrillation should be treated by rate control and anticoagulation.

MANAGEMENT[3]

The management is the same for atrial flutter and fibrillation.

Objectives

1. Cardioversion to sinus rhythm either through a DC cardioversion or through pharmacological (through the use of drugs) cardioversion provided indications for either one or the other are met.
2. Rate control. The ventricular rate is reduced through the use of appropriate drugs to less than 100 beats per minute preferably close to 80 beats per minute. In atrial fibrillation, this invariably abolishes the apex-pulse deficit.
3. Anticoagulation to prevent thromboembolism.
4. In critically ill patients, causes outside the heart may precipitate atrial fibrillation. These include hypoxia, pH, fluid and electrolyte abnormalities, pulmonary embolism and thyrotoxicosis. Unsuspected cardiac causes include mitral valve disease, a recent silent myocardial infarct or myocardial ischemia and pericardial disease. A quick but careful evaluation should unearth and help treat these underlying precipitating or causative factors.

Emergency Management

Patients with atrial flutter or atrial fibrillation with fast ventricular rate, who are in hemodynamic collapse or on the verge of hemodynamic collapse, need emergency electrical cardioversion.

Direct Current Cardioversion

Atrial flutter can generally be converted with a synchronized DC shock energy as low as 50 J. Many prefer to use 100 J as it is invariably successful in cardioversion.

In recent onset atrial fibrillation, sinus rhythm can be restored by a DC shock 100 J, though here again many could prefer to start with an initial energy level of 200 J or greater. Patients with chronic obstructive lung disease or obese individuals may require a higher setting at 300–350 J.

Direct current cardioversion is a painful procedure, so that premedication with midazolam or fentanyl is indicated. Each shock should be synchronized with the R-wave of the QRS complex to prevent electrical stimulation in the vulnerable phase of ventricular repolarization, which usually coincide with peak of the T-wave.

Rate Control

Rate control is important and relevant for all atrial tachyarrhythmias, particularly if restoration of sinus rhythms is not desirable or is deferred.

Intravenous diltiazem, verapamil, beta blockers can control the ventricular response in atrial fibrillation with a fair degree of rapidity. The efficacy of rate control is however less marked in atrial flutter than in atrial fibrillation. There is a 20–30% decrease in the ventricular rate, 20–30 minutes to maximal effect, and 12–25% adverse reactions with each of the above drugs.

The use of beta blockers, like metoprolol or esmolol, for rate control is preferable and particularly useful in patients with recent myocardial infarction, in postoperative atrial fibrillation and when thyrotoxicosis is suspected to be the cause of the tachyarrhythmias.

Intravenous amiodarone[7] is also used for rate control; it also converts atrial fibrillation to sinus rhythm in some patients. It is often used as the drug of choice in critically ill patients with organic heart disease and in the postoperative period following cardiac or cardiothoracic surgery. Its advantage over the calcium antagonists and the beta blocker is that it has less of a negative inotropic effect on the heart.

Digoxin given intravenously used to be the treatment of choice for rate control in earlier years. It is no longer so because of the delayed onset of its therapeutic effect which reaches its peak as long as 4–6 hours after its administration. However, digoxin has a positive inotropic action, it may be safer to use in patients with poor ventricular function who have a moderately fast heart rate. Also, digoxin may convert atrial flutter to atrial fibrillation, in which control of the ventricular rate is easier to achieve.

Digoxin for rate control is given IV in a dose of 0.25 mg and repeated 6 hourly till a maximum dose of 0.75–1 mg is administrated.

Digoxin may not be effective in the control of a fast ventricular rate in the presence of high fever, acute infection and thyrotoxicosis. Digoxin is also ineffective and may produce a paradoxical increase in the ventricular rate when atrial fibrillation complicates the Wolff-Parkinson-White syndrome. Failure of digitalis to act or an increase in the ventricular rate after its use should therefore always suggest an underlying Wolff-Parkinson-White syndrome.

Pharmacological Conversion

If atrial fibrillation or flutter is hemodynamically stable and of recent onset, pharmacological conversion is often effective and should be attempted.

The only drug for pharmacological conversion easily available in India is amiodarone.[7] Amiodarone is preferably given through central line in a dose of 5 mg/kg over 30–60 minutes followed by infusion of 15–20 mg/kg for a total of 24 hours generally not exceeding a total of 1–1.2 g. The drug is given orally in a dose of 200 mg thrice daily from the next day, the IV infusion being stopped by the third or fourth day. A maintenance dose of 200 mg once or twice daily may be required to prevent a recurrence.

Pharmacological conversion of atrial fibrillation can perhaps be better accomplished (compared to amiodarone) with the IC class of antiarrhythmic drug—flecainide and propafenone[8] administered orally as a single dose of 300 mg and 600 mg respectively. The efficacy of these drugs for conversion to sinus rhythms is 60–80%. Both oral and IV routes of administration are equally effective; IV administration results in a quicker conversion to sinus rhythms. Both these IC drugs significantly slow the atrial rate to 300–350 beats per minute; this can result in a 1:1 AV conduction. Hence, calcium channel blockers (verapamil and diltiazem) or beta blockers which exert a blocking effect on AV nodal conduction should be used concomitantly with these IC drugs.

Class IC drug are ineffective for the conversion of atrial flutter to sinus. They may prolong the cycle length by slowing conduction, but they do not break the flutter circuit.

The class III agent ibutilide[9] is the drug of choice for terminating atrial flutter. It is administered in dose of 1–2 g intravenously over 10 minutes and has a success rate of 60%. Its adverse effects are a prolonged QT with a risk of torsades de pointes.[10] Higher doses of ibutilide—two successive IV infusions of 1 g are usually required to terminate atrial fibrillation. Ibutilide can achieve conversion to sinus rhythms in patients who persist with atrial fibrillation or flutter for as long as 30 days. The success rate of conversion in these circumstances drops to 20–30%.

Neither the class IC nor the class III agent ibutilide are easily available in our country. Table 1 lists the drugs, their dosages and their adverse effects.

Atrial Pacing

Over drive pacing can terminate atrial flutter in the majority of cases. It is particularly feasible after cardiac surgery when patients have already epicardial pacing wires in place or in patients with dual chamber pacemakers and defibrillators. Overdrive pacing may however at times induce atrial fibrillation. This is usually short-lived and is generally followed by sinus rhythm.

Anticoagulation

Anticoagulation is mandatory if atrial flutter or fibrillation persists for more than 24–48 hours or if the duration is unknown. The danger of thromboembolic complications is equal in both flutter and fibrillation. In patients who are hemodynamically stable with either atrial flutter or fibrillation of more than 48 hours duration, rate control and 3 weeks anticoagulation with warfarin (INR 2–2.5) are necessary before intervention by DC conversion or pharmacological conversion is attempted.[11]

If for any reason cardioversion cannot be deferred, transesophageal echocardiography[12] should be done for the presence of thrombi in the atria or ventricles; short-term anticoagulation with low molecular weight heparin is reported to be both safe and effective.

Post-cardioversion anticoagulation should be given if atrial fibrillation has been present for 48 hours or more or if thromboembolic risk factors are present (Table 2 and Flowchart 1).[11,13]

Table 1: Antiarrhythmic drugs for pharmacologic conversion of atrial tachyarrhythmias (flutter, fibrillation)

Drug	*Route of administration*	*Dose*	*Potential adverse effects*
Flecainide	Oral or intravenous	Loading oral dose 200–300 mg or slow injection 1.5–2 mg/kg over 10–20 min; if no response, infusion 1.5 mg/kg for 1 h, then 0.1–0.25 mg/kg over 24 h	Rapidly conducted atrial flutter, possible deterioration of ventricular function in the presence of organic heart disease, monomorphic ventricular tachycardia
Propafenone	Oral or intravenous	Loading oral dose 450–600 mg or 1.5–2 mg/kg IV over 10–20 min, followed by infusion 5–10 mg/kg if needed	
Ibutilide	Intravenous	1 mg over 10 min; if no response, additional 1 mg	QT prolongation, torsades de pointes, hypotension
Amiodarone	Intravenous (preferably central line)	5–7 mg/kg over 30–60 min, followed by infusion 20 mg/kg for 24 h (total 1,200–1,800 mg)	Hypotension, bradycardia, QT prolongation, torsades de pointes (?), gastrointestinal upset, constipation, phlebitis
Procainamide	Intravenous	100 mg IV every 5 minutes until the cardiac dysrhythmia is controlled or the total dose reaches about 15 mg/kg	QRS widening, torsades de pointes, rapid atrial flutter

Table 2: Risk stratification and indications for anticoagulation in atrial fibrillation and flutter

Risk of stroke	*Definition*	*Therapy*
Low (1%/yr)	Age <65 yr; ejection fraction ≥0.50; no stroke or transient ischemic attack, hypertension, heart failure, or valvular heart disease	Aspirin 325 mg
Low to moderate (1.5%/yr)	Age 65–75 yr; no risk factors	Aspirin 325 mg
Moderate to high (2.5%/yr)	Age 65–75 yr and either diabetes or coronary heart disease	Warfarin (INR 2.0–3.0)
High (6%/yr)	Age <75 yr and hypertension, heart failure, or ejection fraction <0.50	Warfarin (INR 2.0–3.0)
	Age >75 yr, particularly women, even in the absence of risk factors	
Very high (10%/yr)	Age >75 yr and hypertension, heart failure, or ejection fraction <0.50	Warfarin (INR 2.0–3.0)
	Any age with a history of stroke or transient ischemic attack or valvular heart disease	

Abbreviation: INR, International Normalization Ratio.
Source: Modified from Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: scientific review. JAMA. 2002;288:1388-95.

ACCELERATED ATRIOVENTRICULAR (NODAL) RHYTHM

Nodal or Junctional tachycardia is caused by abnormal automaticity in the AV node. The QRS complex due to ventricular depolarization is narrow with the ventricular rate ranging between 80 and 250 beats per minute. There is AV dissociation because the atria continue to be activated by the sinus node while the ventricles are activated by the ectopic junctional site. The commonest cause of this abnormal rhythm is digitalis toxicity. Normal rhythm is restored if digitalis is withdrawn. If the rate of impulse formation within the AV node is not too fast, atropine administered intravenously increases the discharge rate from the sinus node and allows it to take charge of the normal impulse formation and conduction of the cardiac impulse. AV junctional tachycardia is also a feature of the sick sinus syndrome, which may well need to be countered by the insertion of a dual chamber pacemaker.

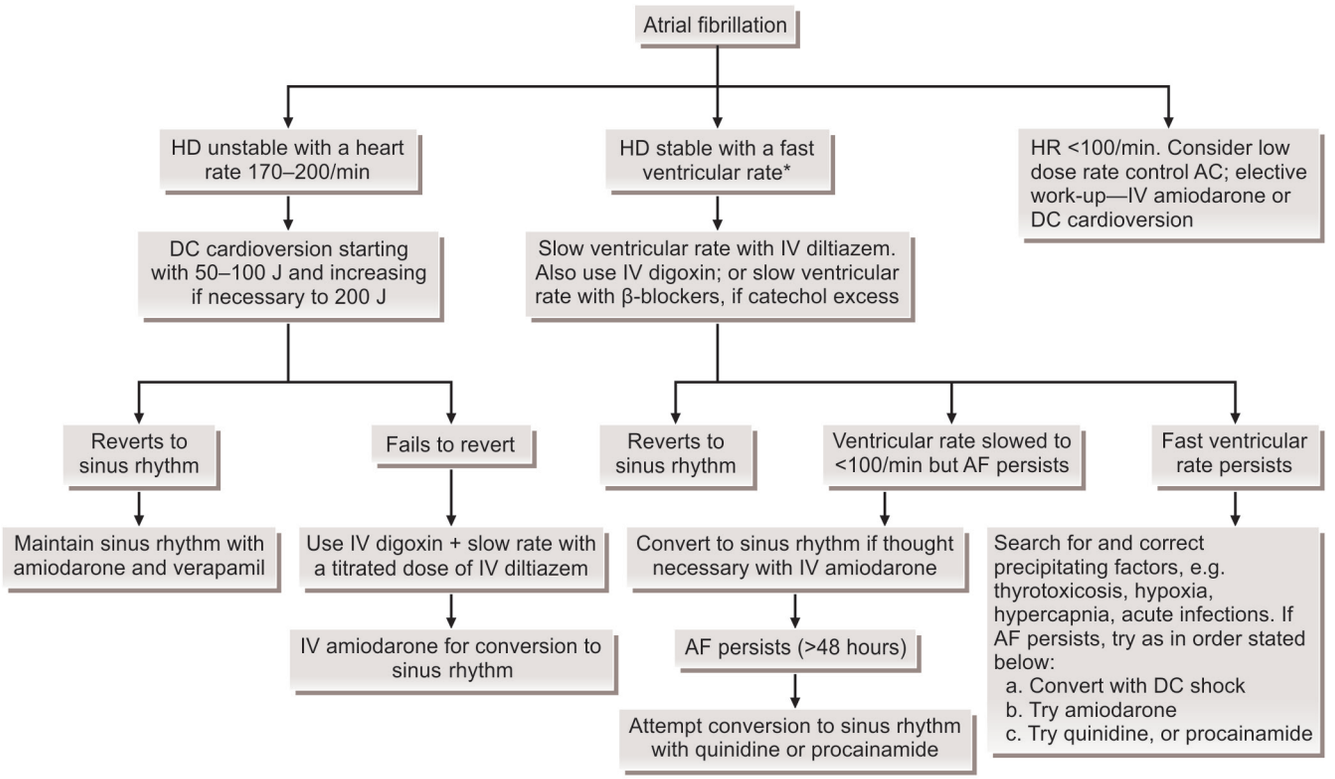
ATRIAL TACHYCARDIA

Paroxysmal atrial tachycardia is generally due to enhanced automatic activity within the atrial ectopic focus discharging regularly at 120–250 beats per minute. Generally, the rate is below 200 beat per minute. Paroxysmal atrial tachycardia can also be due to triggered activity or intra-atrial re-entry.

Electrocardiographic Pattern

The P-waves precede the narrow QRS complex and the PR interval is longer than observed in normal sinus rhythm, the P-wave morphology being different from that observed in sinus rhythm. The P-wave morphology depends on the site of origin of the atrial ectopic focus. When the ectopic focus is within the left atrium, the P-waves are negative in lead I, avL, V_5, V_6.

Flowchart 1: Algorithm for the management of atrial fibrillation


Atrial fibrillation
HD unstable with a heart rate 170–200/min
HD stable with a fast ventricular rate*
HR <100/min. Consider low dose rate control AC; elective work-up—IV amiodarone or DC cardioversion
DC cardioversion starting with 50–100 J and increasing if necessary to 200 J
Slow ventricular rate with IV diltiazem. Also use IV digoxin; or slow ventricular rate with β-blockers, if catechol excess
Reverts to sinus rhythm
Fails to revert
Reverts to sinus rhythm
Ventricular rate slowed to <100/min but AF persists
Fast ventricular rate persists
Maintain sinus rhythm with amiodarone and verapamil
Use IV digoxin + slow rate with a titrated dose of IV diltiazem
Convert to sinus rhythm if thought necessary with IV amiodarone
Search for and correct precipitating factors, e.g. thyrotoxicosis, hypoxia, hypercapnia, acute infections. If AF persists, try as in order stated below:
a. Convert with DC shock
b. Try amiodarone
c. Try quinidine, or procainamide
IV amiodarone for conversion to sinus rhythm
AF persists (>48 hours)
Attempt conversion to sinus rhythm with quinidine or procainamide

*Many units use IV amiodarone in a bolus dose of 300 mg followed by an infusion of 750 mg as the first choice in preference to IV diltiazem and digoxin.

Acute Management

Patients in whom atrial tachycardia is associated with a high ventricular rate (>200 beats per minute) may show hemodynamic stress or even failure particularly if they are old or have underlying heart disease. DC cardioversion converts atrial tachycardia to sinus rhythm, if the tachycardia is based on triggered activity or on re-entry mechanism. However, it may not terminate automatic tachycardias. Atrial overdrive pacing may slow the rate, but generally does not suppress the automatic ectopic focus.

Verapamil and beta blockers can either terminate the tachycardia or can produce good rate control. Quinidine 0.4 g every 2 hours for 3–4 doses is also effective in conversion to sinus control, but unfortunately, this drug is no longer available.

Flecainide, sotalol and amiodarone are also effective in converting to sinus rhythm.

ATRIAL TACHYCARDIA WITH ATRIOVENTRICULAR BLOCK

Atrial tachycardia with an atrioventricular block is classically due to digitalis toxicity. It may however also occur in patients with organic heart disease.

If atrial tachycardia with a 2:1 block is due to digitalis toxicity, the drug is stopped. Potassium should be administered in a slow 5% dextrose infusion.

MULTIFOCAL ATRIAL TACHYCARDIA

This is an irregularly irregular rhythm caused by a rapid irregular atrial activity with P-waves of varying morphology and varying PR intervals. It is typically observed in chronic obstructive pulmonary disease particularly when there has been an overuse of theophylline and β_2 agonists.[14,15]

Management

1. Theophylline is discontinued. This in itself can restore sinus rhythm in some patients.[15]
2. Intravenous magnesium sulfate may prove effective. The protocol suggested is 2 g magnesium sulfate in 50 mL saline over 15 minutes followed by 6 g of magnesium sulfate in 500 mL saline over 6 hours.[16] In one study, use of the above protocol led to conversion of multifocal atrial tachycardia to sinus rhythm in close to 90% of patients. The mechanism of action is unknown.
3. Correct hypomagnesemia and hypokalemia if they exist. Hypomagnesemia must be corrected before hypokalemia.

4. Intravenous verapamil in a dose of 100 μg/kg IV either slows the tachycardia, exerting rate control or converts to sinus rhythm in 50% of cases.[17] Metoprolol in a dose of 5 mg IV repeated if necessary at 5 minute interval to a maximum of 15 mg is also effective in converting multifocal atrial tachycardia to sinus rhythm. Metoprolol is however best avoided in patients with COPD where unfortunately this rhythm disturbance is most frequently observed.

WIDE COMPLEX (QRS >0.12 S) TACHYARRHYTHMIAS

These chiefly include VT and torsade de pointes, which in fact is an unusual or peculiar form of polymorphic VT. SVTs with delayed or aberrant conduction can also produce wide QRS complexes (>0.12 s), which are difficult to distinguish from VTs. As a matter of principle, it should be remembered that VT probably causes more than 95% of wide complex tachycardias in patients who have underlying cardiac disease. Therefore, in an ICU setting a wide QRS complex should be taken as VT unless proved otherwise.

There are a number of ECG features which help to distinguish VT from SVT with delayed or aberrant conduction, and these are tabled in Table 3.

The features of note are as follows—
In a long-rhythm strip, the presence of fusion beats, capture beats, and/or AV dissociation in a wide QRS tachycardia, point to a VT.

In a 12-lead ECG, VT is more likely if: (1) in the presence of a right bundle branch block pattern, the pattern in V_1 is monophasic. If it is biphasic, then R is taller than r'; small r and large S-waves or a QS pattern is present in V_6; (2) in the presence of a left bundle branch block pattern, the axis is to the right, the QRS is wider than 0.16 seconds, and V_6 shows a small q and a low amplitude R-wave, or a QS pattern; (3) QRS complexes are similar in V_1–V_6, either all positive or all negative.

Table 3: Differentiating features between ventricular tachycardia and supraventricular tachycardia (SVT) with delayed or aberrant conduction

SVT with delayed or aberrant conduction	*Ventricular tachycardia*
Slowing or termination by increase in vagal tone	Fusion beats present Capture beats present
Premature P-waves present at onset	Atrioventricular dissociation present QRS duration >140 ms
PR interval <100 ms	Left axis deviation often present
QRS duration usually <120 ms	QRS complexes: specific QRS patterns often seen in precordial leads (see text)
P and QRS rate and rhythm often linked to suggest that ventricular activation depends on atrial discharge QRS complexes: rSR' frequently seen in V_1	

VENTRICULAR TACHYCARDIA

Incidence in the Critical Care Setting

A multicenter study[18] involving over 1,341 patients in 26 ICUs over a month revealed that 12% had episodes of sustained arrhythmias—8% with supraventricular arrhythmias, 2% with ventricular arrhythmias and 2% with conduction abnormalities. The in-hospital mortality was 29% in patients with arrhythmias and 17% in those without arrhythmias. A detailed analysis revealed that only ventricular arrhythmias were associated with increased mortality. Supraventricular arrhythmias and conduction abnormalities were instead markers of severity of illness and did not independently contribute to the risk of death.

Diagnosis

Ventricular tachycardia is a dangerous tachyarrhythmia characterized by a series of three or more ventricular ectopic impulses (wide QRS complexes) at a rate of 100 or more beats per minute. *Accelerated ventricular rhythm* is defined as a ventricular rhythm occurring at 50–100 beats per minute. Identifying the rhythm is important. Accelerated ventricular rhythm usually indicates ischemic heart disease and antiarrhythmic treatment for this rhythm disturbance is not necessary. VT can be brief, subsiding within 30 seconds (non-sustained VT), or it can last for longer periods (>30 s) of time (sustained VT). The most frequent and the most likely cause of VT is myocardial ischemia or a recent myocardial infarction. Other organic heart diseases complicated by VT include aortic valve disease, cardiomyopathies and VT following coronary artery bypass surgery, particularly after aneurysmectomy or aneurysmorrhaphy of a ventricular aneurysm.

Ventricular Fibrillation

Ventricular fibrillation is characterized by irregular wave forms of varying duration, contour, amplitude without identifiable QRS and T-waves. VF (and pulseless VT) are akin to cardiac arrest and cause unconsciousness within seconds. Generalized seizures, and agonal breathing follow; death occurs unless promptly diagnosed and treated.

In an ICU setting, VT can also occur in the absence of serious organic heart disease. It is important to look for potentially reversible factors, which may initiate or perpetuate serious ventricular arrhythmias. Important reversible conditions causing sustained VT have been listed in Box 1.

These factors include hypoxia, hypercapnia, hypoglycemia, hypokalemia, hypomagnesemia, hypocalcemia, excessive use of inotropes (catecholamines) or excessive endogenous catecholamine production, hyperthyroidism, drug toxicity

Box 1: Potentially reversible causes of ventricular tachycardia

- Ischemic heart disease
- Hypoxia/hypercapnia
- Acidosis
- Electrolyte abnormalities—Hypokalemia, hypocalcemia, hypomagnesemia
- Hyperthyroidism
- Excess of circulating catecholamines—Endogenous/exogenous
- Drug toxicity—particularly digitalis
- Presence of intracardiac catheters

(commonly produced by antiarrhythmic drugs), digitalis toxicity and the presence of intracardiac catheters.

The initial workup should therefore include measurements of serum electrolytes, calcium, magnesium, arterial pH, blood gas analysis and cardiac enzymes. If the patient has an indwelling catheter, e.g. a Swan-Ganz catheter or a central venous line, it is important to check with an X-ray that it does not lie within the right ventricle.

Management of Ventricular Tachycardia

Premature ventricular contractions (PVCs) and episodes of non-sustained VT have no immediate hemodynamic significance. Management consists of a proper assessment, identification and removal of factors that may contribute to these episodes. The risk of evolving into sustained VT increases if PVCs are very frequent, occur in pairs or triplets, or exhibit the R on T phenomenon, particularly when this is observed in the ICU, against a background of ongoing myocardial ischemia, myocardial infarct or in patients with poor left ventricular function. Under these circumstances, and more so if frequent PVCs and ill-sustained episodes of VT appear to precipitate angina or hemodynamic instabilities, IV 150–300 mg of amiodarone given over 20 minutes, followed by an infusion of 750 mg amiodarone over 24 hours may well be justified. Oral amiodarone 200 mg TDS is started so as to overlap the IV infusion. Patients with on-going ischemia or a recent infarct are often hyperadrenergic. Besides attending to reperfusion, beta blockers given orally may also control frequent PVCs or frequent episodes of non-sustained VT. In general, however, non-sustained VT occurring in asymptomatic patients without underlying heart disease require no specific therapy.

Management of Sustained Ventricular Tachycardia

Patients in severe hemodynamic failure and collapse characterized by marked hypotension, or acute heart failure, or patients who have pulseless VT, polymorphic VT, and VF should promptly receive unsynchronized electric shocks and advanced cardiac life support.

Direct current unsynchronized cardioversion should be given with an initial shock of 100 J followed by repetitive shocks of 200, 300 and 360 J if necessary. These critically ill patients would almost certainly die if not for prompt cardioversion and advanced cardiac life support (see Chapter Cardiopulmonary Resuscitation and Cerebral Preservation in Adults).

- Any patient with a wide QRS complex tachycardia, who shows evidence of hemodynamic instability, should also be converted by DC cardioversion. One does not want a hemodynamic collapse in these patients before using cardioversion, which is considered the most effective form of therapy, to revert VT to sinus rhythm. IV midazolam or fentanyl need to be used as premedications.
- In patients with monomorphic VT who are hemodynamically stable, the intensivist needs to—
  - Identify as far as possible arrhythmogenic factors that could trigger VT and sustain VT in a particular patient. The factors commonly present in critically ill patients are—
    - Acid base and electrolyte abnormality.
    - Hypoxia, hypercapnia, hemodynamic abnormalities.
    - Use of pro-arrhythmogenic drugs.
    - A prolonged QT interval.
    - Hyperadrenergic states. Use of inotropic drugs, like dopamine or dobutamine, which in some patients might induce VT even when not used in excess.
    - An underlying myocardial infarct or active myocardial ischemia.
    - Mechanical stimulation of the myocardium as by a central line within the right ventricle or a pulmonary artery catheter abutting against the wall of the right ventricle.

    Treatment of arrhythmogenic factors outlined above in itself can terminate an arrhythmogenic episode or at least prevent its recurrence. In particular, stress should be given to correction of electrolyte imbalance, treatment of myocardial ischemia, discontinuation of drugs that prolong the QT interval and reducing or omitting drugs, which increase adrenergic stimulation or have an inotropic action. Repositioning a central venous pressure line or a misplaced pulmonary artery catheter may well abort an attack or prevent its recurrence.
  - Decide on the method to revert the VT to sinus rhythm.

    Both DC synchronized cardioversion and the IV administration of antiarrhythmic drugs are equal first-line options. Antiarrhythmic drugs are generally preferred as anesthesia is not necessary and their antiarrhythmic effects persist after the reversion of VT to sinus rhythm.

    The antiarrhythmic drug of choice is amiodarone[19] given in a dose of 5 mg/kg IV over 20 minutes followed by an IV infusion of 750 mg to 1 g over the next 24 hours. An IV infusion of 500–750 mg given over the next 2 to 3 days may be necessary. Oral amiodarone

in a dose of 200 mg thrice daily is given as a preventive once the rhythm has reverted.

Amiodarone should also be administered to patients with sustained monomorphic VT who are refractory to conversion after electric shocks .

Lidocaine was the drug of choice for VT before the advent of amiodarone, which has by and large replaced lidocaine. However, even today in patients in whom stable monomorphic VT is associated specifically with unstable angina or myocardial infarction, lidocaine is considered by some authorities to be a reasonable initial choice.[20] Lidocaine is administered in a bolus of 75 mg; a bolus of 50 mg may be repeated if necessary after 5 minutes. This is followed by an IV infusion of the drug at 1–2 mg/hour for continued control. The drug is metabolized by the liver and is avoided in patients with liver cell dysfunction. Lidocaine toxicity chiefly involves the central nervous system—drowsiness, agitation, confusion, muscle twitching and generalized seizures may occur. These are chiefly observed in elderly people or when larger doses are being used. The drug can also cause bradycardia, hypotension and sinus arrest. Liver cell dysfunction may also occur.

The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2006 guidelines[21] for the management of ventricular arrhythmias recognize various drugs besides amiodarone and lidocaine. These drugs include procainamide, flecainide and propafenone. None of these drugs are easily available in our country and probably have no advantage over amiodarone and lidocaine. In Europe, IV procainamide is often used as the initial choice for patients with stable sustained monophasic VT. Procainamide when used is given at a rate of 20 mg/minute until the arrhythmia reverts or a total not exceeding 1,000 mg is administered. Hypotension and a prolonged QT are dangerous side effects. The prolonged QT can result in a drug induced VT. Hypotension may necessitate stoppage of the drug. The drug is contraindicated in patients with a prolonged QT interval. We have stopped using this drug for several years; also, the drug is not easily available in the country.

Whenever one uses amiodarone or lidocaine or any other antiarrhythmic drug, it is now felt that the addition of a second antiarrhythmogenic drug should be discouraged as the proarrhythmic effects of two drugs are compounded. Thus, if the use of the single agent in optimal doses fails to revert VT, it is best to proceed to DC synchronized electrical cardioversion rather than use a second drug. Monophasic wave form electric shocks at an initial energy level of 100 J are generally effective. Comparable energy levels may be effective when using biphasic wave form electric shocks.

- *Transvenous over-drive spacing* is also used for terminating monophasic VT if there is refractoriness to cardioversion or VT recurs despite the use of antiarrhythmic drugs.
- *Ventricular arrhythmias with cessation of effective blood flow.*

  As mentioned at the start, the patient should be immediately cardioverted using an unsynchronized DC shock—200 J from a defibrillator providing bi-wave form and 360 J if the defibrillator provides a monophasic wave form. Following shock delivery, the patient should receive prompt advanced cardiac life support according to the most recent guidelines for cardiopulmonary resuscitation and emergency cardiovascular care.[22] A 1-shock strategy followed by prompt chest compression is now recommended to minimize interruption in chest compression. The shock is repeated every 3–5 minutes if VT or VF persists (see Chapters Cardiopulmonary Resuscitation in Infants and Children, and Cardiopulmonary Resuscitation and Cerebral Preservation in Adults).

The following points are worthy of note—

- Survival after pulseless VT or VF is inversely related to the time elapsed between onset of arrhythmia and the delivery of electric shocks.[23] The survival rate is high when duration of untreated VF is less than 4 minutes.
- With more protracted untreated VF, evidence suggests that a period of closed chest resuscitation before attempting defibrillation could improve outcome.[24,25]
- For patients with shock, refractory or pulseless VT, use of amiodarone may well improve chances of restoration of cardiac activity.[26]

Electric storm is a highly lethal form of VT occurring chiefly during the course of myocardial infarction. Amiodarone, lidocaine, procainamide fail to secure a stable sinus rhythm. The VT also continues to recur again and again even after several DC shocks. The underlying mechanism seems to be related to excessive unbalanced sympathetic activity. It has been recently shown that sympathetic blockade, using IV beta blockers or stellate ganglion blockade is successful in restoring a stable sinus rhythm, thereby dramatically improving the outcome.[27]

TORSADE DE POINTES[28]

Torsade de pointes is a polymorphic VT characterized by wide QRS complexes that change in amplitude and appear to be twisting round the isoelectric line of the ECG—some complexes being above the isoelectric line and others below. This arrhythmia is associated with a prolonged QT, which may be congenital or acquired. The acquired form is caused by electrolyte disturbances and drugs. Drugs chiefly involved are psychotropic drugs, antiarrhythmic drugs, macrolides and quinolones. Electrolyte disorders that can cause torsade de pointes are hypokalemia, hypomagnesemia and hypocalcemia.

Polymorphic VT can also be associated with a normal QT—it is then not termed torsade de pointes but just called polymorphic VT.

Management

Management is guided by the QT interval.

$$QT_c = QT/\sqrt{RR}$$

Where, QT_c = corrected QT interval for rate
QT is the measured QT interval and √RR is the square root of the RR interval.

A prolonged QT_c is defined as a QT_c greater than 0.44 seconds.

Polymorphic VT with a normal QT interval responds to the standard antiarrhythmogenic agents like amiodarone and lidocaine.

Management in patients with a prolonged QT depends on whether the prolongation is congenital or acquired. If the QT prolongation is acquired the treatment is as follows—

- Administration of IV magnesium sulfate starting with 2 g IV over 1 minute, the dose being repeated 10 minutes later if needed.
- Correction of electrolyte abnormalities. It is to be noted that hypokalemia and hypocalcemia may be due to an underlying magnesium deficiency even if serum magnesium levels are normal. Magnesium replacement is therefore of critical importance in patients with hypokalemia and hypocalcemia.
- Discontinuation of drugs that prolong the QT interval.
- Overdrive pacing and the use of beta blockers after pacing.

If the QT prolongation is congenital, beta blockers and implantation of an internal cardioverter defibrillator device should be considered.

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CHAPTER 24

Bradyrhythms and Heart Block in the ICU

INTRODUCTION

Bradyrhythms in the intensive care unit (ICU) may be harmless or may portend disaster. They are due to slowing of impulse formation, or a delay in impulse conduction through one or more areas of specialized conducting tissue that propagate the cardiac impulse. A bradyrhythm may be totally asymptomatic. Yet in patients with intrinsic heart disease or in ICU patients admitted for other serious problems, a marked fall in heart rate reduces the cardiac output. This is invariably so if the heart rate falls below 45 beats per minute. A fall in cardiac output is certain to cause a further deterioration in an already seriously ill patient. The rate should be corrected before such a deterioration is clinically observed. Symptomatic bradyrhythms, whatever the etiology, need immediate treatment.[1]

A bradyrhythm is defined as a cardiac rhythm slower than 60 beats per minute.

Bradyrhythms are divided into two major categories—

1. Disturbance in sinus impulse formation and conduction [sinus bradycardia, sinoatrial (SA) block, a Wenckebach block in the SA node, sinus arrest, the sick sinus syndrome].
2. Atrioventricular (AV) block. The term is applied to a delay in conduction in the AV node or in the infranodal conduction tissue. Delayed conduction in infranodal tissue is of far greater prognostic import compared to conduction delay within the AV node itself.

SINUS BRADYCARDIA

In the ICU, this condition is observed chiefly in the sick sinus syndrome or in ischemic heart disease, particularly after an acute inferior myocardial infarction. It can also occur in patients with no organic heart disease—chiefly due to increased intracranial tension, hypothyroidism, to hyperactive vagal reflexes and to drugs. An important example of increased vagal tone is in patients with tetanus. These patients, when undergoing a tracheal suction, may show marked bradycardia that may culminate in cardiac arrest. The above-mentioned problem is also occasionally observed in other critical illnesses. Numerous drugs can also produce sinus bradycardia (chiefly digitalis and beta-blockers).

The following problems can arise as a result of marked sinus bradycardia—

- *A low output state* This may occur suddenly or over a period of time. A slow rate can also produce faintness or syncope.
- *A potentiation of ventricular ectopics* The unfortunate use of antiarrhythmic drugs in an attempt to suppress these ectopics, further slows the heart. Greater ectopic activity is then often observed, and this may lead to ventricular tachycardia or fibrillation. On the other hand, increasing the ventricular rate may abolish ventricular ectopics.

SINOATRIAL BLOCK

A second degree SA block[2] is evident on the monitor or on a rhythm strip, as a long pause between two sinus impulses. A Wenckebach type of SA block is characterized by a progressive shortening of the PP intervals until a long pause occurs because of the blocked beat. A third degree SA block leads to atrial and ventricular standstill, and if this is sufficiently long, a nodal or ventricular escape rhythm is noticed. SA block occurs after excessive vagal stimulation, in inferior myocardial

infarction, acute myocarditis or as a side effect or a toxic effect of drugs like digitalis, propranolol and other antiarrhythmic drugs. It also occurs as part of a sick sinus syndrome, which may manifest as a bradyrhythm due to SA block or even an AV block. Bradytachyrhythms are also often observed with a sick sinus syndrome.

One of the most important causes of SA block (and later an AV block as well) in critically ill ICU patients is hyperkalemia. Hyperkalemia should always be thought of in a patient with a bradyrhythm. The P-waves are absent and the QRS complexes are slow and wide, followed by tall T-waves. A bundle branch block pattern (without preceding P-waves) is sometimes observed. The possibility of hyperkalemia is particularly important in patients with renal insufficiency, or in those on chronic dialysis, particularly if the patient is on ACE inhibitors.

MANAGEMENT

The following points should be noted—

- All drugs that slow the heart rate should be omitted.
- If the bradyrhythm in a critically ill patient falls well below 50 beats per minute, the rate should be increased by drugs. It does not matter whether the bradyrhythm is due to organic heart disease or occurs in other critical illnesses.
- If the bradyrhythm produces a low output state or if an SA block produces faintness or syncope, or is complicated by ventricular ectopics, the basic heart rate should be increased with atropine or isoprenaline, or if needs be, by transvenous cardiac pacing.

Atropine is administered slowly intravenously in a dose of 0.3–1 mg.

In an emergency, isoprenaline is given in an infusion of 1 mg in 500 mL dextrose. The infusion rate is initially kept at 1–4 µg per minute and is carefully increased till the desired effect on the heart rate is achieved. The patient should be carefully monitored for ectopics that may be induced by isoprenaline.

When a symptomatic bradyrhythm persists, or when it fails to respond to drugs, or when the use of drugs produces toxic effects (isoprenaline induced ventricular ectopics or tachycardia), transvenous pacing should be done. Many units would opt for transvenous pacing in symptomatic bradyrhythms or bradyrhythms which cause a low output state without taking recourse to drugs.

When severe persistent bradycardia occurs in acute inferior myocardial infarction and does not respond to atropine, a temporary transvenous pacing is the method of choice to increase the heart rate. Isoprenaline should be avoided in these circumstances, except as a temporary emergency measure; this drug increases myocardial oxygen consumption and thereby can cause an extension in the area of infarction.

If hyperkalemia is strongly suspected as the cause of a SA block, a blood sample is quickly sent for serum K^+ estimation. Between 10–20 mL of 10% calcium gluconate is given intravenously without waiting for the result. This is followed by a dextrose-insulin infusion as detailed in the Section Fluid and Electrolyte Disturbances in the Critically Ill.

ATRIOVENTRICULAR BLOCK

All forms of AV block[3] can be either nodal or infranodal. Infranodal blocks can be intra-Hisian or infra-Hisian and are far more dangerous than nodal blocks.

A first degree AV block is characterized by a prolonged PR interval. It needs no treatment,[4] except careful assessment whether drugs known to produce a first degree AV block can be reduced or omitted. Digitalis is the commonest cause of prolonged AV conduction. Other antiarrhythmic drugs can also do the same.

Second degree AV block of the Wenckebach type (the block in most cases is nodal and not infranodal) is characterized by progressive prolongation of the PR interval with a progressive shortening of the RR interval, till a P-wave is blocked at the AV node and does not produce a ventricular QRS complex. A Wenckebach type of AV block does not constitute a problem, except when it is a forerunner of a high grade block.[5] This is typically observed in some patients with acute inferior myocardial infarction.

A Mobitz type II AV block is of ominous significance as the site of the block is infranodal. It is associated with a sudden block of the P-wave occurring sporadically in an otherwise normal rhythm, or is characterized by a regular 2:1 or 3:1 block at the AV node. It often precedes a high grade or complete AV block and is at times a forerunner to sudden death.

The most important causes of second degree AV block are myocardial infarction, acute myocarditis and drugs—particularly digitalis, quinidine and procainamide.

Atropine may be used for a Wenckebach block. A Mobitz type II block needs prompt transvenous pacing to forestall a possible catastrophe.[4]

Complete or third degree AV block[2] is characterized by a very slow ventricular rate of close to 30 beats per minute, with a total dissociation between the atria and the ventricles. All impulses reaching the AV node are blocked, and the ventricles beat from a focus within the AV node, or from a focus below the AV node. AV dissociation with a ventricular rate greater than 40 beats per minute cannot be called a complete AV block, though a high-grade AV block obviously exists in these patients. Complete or third degree AV block in an ICU setting is observed in acute myocardial infarction, or in drug toxicity, chiefly digitalis toxicity. Most antiarrhythmic drugs used to treat tachyrhythms can also produce a complete AV block as a toxic effect.

Patients with Leriche's disease or Lev's disease, which is characterized by fibrosis of the infranodal conducting tissue, may also find admission to the ICU due to syncopal spells, or to Stokes-Adams attacks occurring against a background of complete AV block. Rarely, acute myocarditis or calcific aortic stenosis may also be associated with a complete AV block.

Hyperkalemia induces both SA block and AV block; the former invariably precedes the latter. Hyperkalemia (serum K^+

>6.5–7 mEq/L) also prolongs the intraventicular conduction, causing slow wide complexes.

Complete AV block with a slow ventricular rate needs emergency transvenous pacing in the ICU.[4]

Complete or high-grade AV block in relation to acute myocardial infarction Acute inferior myocardial infarction often results in a Wenckebach block followed by a high grade, and rarely by a complete AV block. Transvenous pacing should be done for high-grade AV blocks. The block almost always resolves within 7–12 days,[6] with a return to sinus rhythm, when the pacing catheter is withdrawn.

Complete AV block in the presence of acute anterior myocardial infarction is of grave prognostic significance, and carries a high mortality (70–80%).[7] This is because in all such instances there is extensive damage of the anterior wall, the septum and the lateral wall, with ischemic destruction of conducting tissue below the AV node. This may include the bundle of His, the branches of the bundle of His, and the Purkinje conducting fibers as well. As the block is infranodal, ventricular escape rhythms are much slower and more unstable than in patients with heart block due to acute inferior myocardial infarction where the high grade or complete AV block is nodal. The block in acute anterior myocardial infarction is often associated with pump failure, not only because of the marked bradyrhythm, but also because of the extensive myocardial damage. Complete AV block in these patients might occur suddenly, or might be preceded by various combinations of blocks in the branches of the bundle of His. These blocks include: (1) a right bundle branch block with a block in the anterosuperior division of the left bundle branch; (2) a right bundle branch block with a block in the posteroinferior division of the left bundle branch; (3) a left or right bundle branch block pattern; (4) a bilateral bundle branch block, characterized either by a left or right bundle branch block pattern on the electrocardiogram (ECG), with a significantly prolonged PR interval; (5) a trifascicular block which causes an ECG pattern of a bifascicular block with a prolonged PR interval.

Complete AV block needs prompt transvenous pacing. There is a considerable difference of opinion as to which other combinations of blocks involving the bundle of His, need to be paced in acute anterior myocardial infarction. We generally prophylactically pace patients with a bilateral bundle branch block or a trifascicular block. We do not pace those with a right bundle block together with a block in the anterosuperior division of the left bundle branch. We generally pace patients with a right bundle branch block together with a block in the posteroinferior division of the left bundle branch. We do not generally pace a patient who develops an isolated right or left bundle branch block. There are, however, a number of units who would prophylactically pace all or most of these combinations of heart blocks in the His bundle conducting system that have been listed above.

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CHAPTER 25

Antiarrhythmic Drugs Used in the ICU

GENERAL CONSIDERATIONS

It is important to be familiar with antiarrhythmic drugs used in the acute or emergency management of arrhythmias in the intensive care unit (ICU). Antiarrhythmic drugs are double-edged weapons—they can effectively reverse an arrhythmia and salvage a potentially dangerous situation. At the same time, they can themselves produce side effects which could be cardiac or noncardiac. Remarkably enough, cardiac side effects include heart failure and induction of arrhythmias. In other words, antiarrhythmic agents could well produce the very problem that they are supposed to eradicate or suppress. Drug induced or drug aggravated cardiac arrhythmias (bioarrhythmias) are a major clinical problem. In one study, proarrhythmic events occurred in 6.9% of 506 consecutive patients and in 3.4% of 1,268 drug trials for ventricular tachycardia (VT) and ventricular fibrillation (VF).[1] Factors predisposing to such proarrhythmias include the presence of left ventricular (LV) dysfunction, treatment with digitalis and diuretics, and a longer pretreatment QT interval.[2] Antiarrhythmic drugs are therefore of help, but need to be used with caution. As a matter of principle, it is wise not to use multiple antiarrhythmic drugs simultaneously. If more than one antiarrhythmic drug is being used, possible pharmacokinetic interactions between various drugs should be noted (Table 1). It is also important to constantly bear in mind whether an arrhythmia one is treating may not have been actually caused or potentiated by the very drugs used to treat it. Finally, arrhythmias can be precipitated by factors such as hypoxia, hypercapnia, electrolyte and acid-base disturbances. Correction of these factors can restore sinus rhythm and is far more important than the use of antiarrhythmic drugs. In the past, antiarrhythmic drugs were the mainstay in the treatment of arrhythmias. Surgical procedures have now been developed for the treatment of the Wolff-Parkinson-White (WPW) syndrome, supraventricular, ventricular tachyarrhythmias and more recently even for atrial fibrillation. The ability to use catheter devices to deliver radiofrequency energy to circumscribed lesions that can destroy focal areas of arrhythmogenesis (idiopathic VT) or to limbs of macroreentrant (AV nodal reentral tachycardia, AV reciprocatory tachycardia, atrial flutter) or to microreentrant tachycardia (ischemic VT) has revolutionized the management of arrhythmias. Radiofrequency catheter ablation is now the treatment of choice for many of these arrhythmias provided the necessary experience and expertise is available.

For patients who have experienced potentially lethal ventricular arrhythmias, implantable cardioverter defibrillators (ICD) were introduced in the 1980s. In the Antiarrhythmics versus Implantable Defibrillators (AVID)[3] and Cardiac Arrest Study Hamburg (CASH)[4] trials, it was shown that, when compared with amiodarone, survivors of cardiac arrest who had ICDs had a lower incidence of cardiovascular and total mortality.

Table 1: Pharmacokinetic interactions of a few antiarrhythmic drugs

Drugs	*Clearance*
Quinidine	Increased by phenytoin, phenobarbital, rifampicin Decreased by cimetidine, amiodarone
Lidocaine	Decreased by cimetidine, propranolol
Digoxin	Decreased by quinidine, verapamil, amiodarone; Volume of distribution decreased by quinidine
Disopyramide	Increased by phenytoin, phenobarbital, rifampicin
Procainamide	Decreased by cimetidine, amiodarone

Antiarrhythmic drugs today are therefore used only to reduce the frequency of shocks delivered by ICDs in survivors of cardiac arrest or in patients at risk for cardiac arrest. Nevertheless, antiarrhythmic drugs are important for two reasons—(1) Comparatively, few centers in developing countries have units with the experience and expertise to employ methods detailed above; (2) in a critical care setting, antiarrhythmic drugs still play an extremely important role and the intensivist must be familiar with their use.

CLASSIFICATION OF ANTIARRHYTHMIC AGENTS[5]

The most frequently used classification of antiarrhythmic agents is the Vaughan-Williams classification. This classification is as follows—

Class I agents are sodium channel blockers.
Class II agents are beta blockers.
Class III agents are potassium channel blockers.
Class IV agents are calcium channel blockers.

The class I agents are classified into class Ia (sodium and potassium channel blockage; kinetics of onset and offset of sodium channel blockers are intermediate in rapidity). This class includes quinidine, procainamide and dispopyramide. These drugs slow the rate of rise of phase 0, lengthen the refractory period and the width of the monophasic action potential. The class Ib agents are pure sodium channel blockers. They do not slow the rate of rise of phase 0 of the monophasic action potential (MAP) and shorten the MAP duration; the onset and offset of sodium channel blockade are rapid. This class includes lidocaine, mexiletine and tocainide. The class Ic agents are strong sodium channel blockers with slow onset and offset kinetics. This class comprises of flecainide and propafenone.

The class III agents are drugs that block the potassium channels as their chief antiarrhythmic effect. The class includes sotalol, dofetilide, ibutilide, amiodarone and bretylium. Class IV are calcium channel blockers and include diltiazam and verapamil.

Vaughan-Williams classification is simple and easy to use but has one major drawback. This drawback is that the major effect of an agent or drug from one group overlaps with the effect produced by agents from other groups. To give an example, quinidine which is classified as Vaughan-Williams Group I antiarrhythmic agent (sodium channel blockade), also blocks the potassium channel (class III) and may lead to torsade de pointes, a dangerous side effect. To give another example, amiodarone which is classified as a class III antiarrhythmic agent has sodium channel blocking (class I), beta blocking (class II) and potassium channel blocking (class III) properties.

This chapter does not propose to give an account of all old and new antiarrhythmic drugs. It deals with important commonly used antiarrhythmic agents in the ICU. It is important to be perfectly familiar with a few important drugs and use them skillfully rather than grapple with a host of drugs. Table 2 lists the commonly used antiarrhythmic drugs with their dosages and major side effects.

Table 2: Indications, doses, and main adverse effects of some antiarrhythmic drugs commonly used in the ICU

Drug	*Indications*	*Adverse effects*	*Loading dose*	*Maintenance dose*	*Special remarks*
Lidocaine	Emergency treatment of VT of any etiology, especially in AMI and after open heart surgery	CNS-dizziness, seizures, confusion, coma, sinus node depression, aggravates LV dysfunction, myocardial depression and hypotension	1–2 mg/kg IV bolus, repeat 1/2 dose in 30 minutes	1–2 mg/min infusion	–
Mexiletine	Treatment of VT when lidocaine ineffective	Dizziness, nystagmus, confusion, vomiting; CVS–bradycardia, hypotension, worsening of arrhythmia	100–150 mg, IV bolus	2–4 mg/min infusion for first 3 hrs, then 0.5 mg/min; later 200 mg, 8 hourly, orally	–
Quinidine	SVT, VT, ventricular ectopics	Nausea, vomiting, diarrhea; CNS–tinnitus, hearing loss, visual disturbances hemolytic anemia, thrombocytopenia; CVS—various blocks, torsade de pointes, myocardial depression	400 mg 2 hourly for 4–5 doses orally	200 mg 6 hourly orally	Elevated serum digoxin levels
Procainamide	Treatment of VT when lidocaine ineffective; treatment of atrial flutter/fibrillation after AV conduction is blocked/slowed	Hypotension, various heart blocks, VT and myocardial depression	25–50 mg IV over 1 minute, repeated every 5 minutes to max of 1,000 mg	2–6 mg/min infusion	Contraindicated in torsade de pointes where QT prolonged

Contd...

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Drug	*Indications*	*Adverse effects*	*Loading dose*	*Maintenance dose*	*Special remarks*
Amiodarone	VT or SVT refractory to conventional drugs	Hypotension, worsens ventricular arrhythmias, can induce torsade de pointes, aggravates LVF, rise in liver enzymes	5 mg/kg IV over 20 minutes	10 mg/kg/day for 3–4 days	Dose reduced by 25–40% if digoxin being used
Esmolol	Emergency control of ventricular rate in atrial flutter, atrial fibrillation and SVT	Hypotension, heart block, bronchospasm, acute LVF	500 µg/kg/minutes over 1–2 minutes	50–200 µg/kg/minute infusion	Side effects very transient
Verapamil	PAT, AV nodal entry or reciprocating tachycardias; to slow ventricular rate in atrial flutter/fibrillation	Hypotension, LVF, bradycardia, AV block	7.5–10 mg IV over 2–3 minutes	0.125 mg/minute	Contraindicated in heart block, VT, hypotension. Dose of digitalis should be reduced when verapamil is used
Adenosine	Drug of choice for SVT, AV nodal re-entry, reciprocating tachycardia	Transient AV nodal block, flushing, dyspnea	6–12 mg bolus IV		Smaller dose to be used in patients on dipyridamole
Digoxin	Atrial flutter/ fibrillation, SVT	Nausea, vomiting, visual disturbances, induces arrhythmias, particularly in presence of hypokalemia, hypomagnesaemia and renal dysfunction	0.25 mg IV over 5 minutes, repeated 4 hourly till digitalizing dose of 1–1.25 mg reached in 24 hrs	0.25 mg/day	Dose should be reduced when using with quinidine and verapamil. Care to be taken when used with amiodarone

Abbreviations: AMI, acute myocardial infarction; AV, atrioventricular; CNS, central nervous system; CVS, cardiovascular system; ICU, intensive care unit; IV, intravenous; LV, left ventricle; LVF, left ventricular failure; PAT, paroxysmal atrial tachycardia; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

Lidocaine[6]

Lidocaine is an extremely useful class IB antiarrhythmic agent. It depresses depolarization and shortens repolarization in ventricular muscle fibers. It also depresses both normal and abnormal forms of automaticity. It is only effective when given intravenously.

The drug is metabolized in the liver. It has a mean half-life of 1–2 hours in normal subjects, more than 4 hours in patients with uncomplicated myocardial infarction, more than 10 hours in patients with myocardial infarction and associated cardiac failure, and even longer in patients with cardiogenic shock. Severe hepatic dysfunction or reduced hepatic blood flow as in patients with cardiac failure or shock can markedly reduce the metabolism of the drug in the liver. In patients with liver disease, or in those with cardiac failure with low-output states, the dose of the drug should be reduced by one-third to half.

Clinical Indications

Its main indication is the acute or emergency treatment of ventricular arrhythmias of diverse etiology, but particularly those occurring in acute myocardial infarction and after open heart surgery. It is the drug of choice for suppression of ventricular ectopics, sustained VT and symptomatic VT. It should be administered to patients with pulseless VT or VF that is refractory to electrical counter shocks and epinephrine. After VT or VF is terminated, it is advisable to use the drug in a slow intravenous infusion to prevent recurrences of dangerous ventricular arrhythmias. This is particularly imperative in patients with active myocardial ischemia, hypokalemia and myocardial dysfunction. Since most wide QRS complex tachyrhythms are presumed to be ventricular rather than supraventricular, lidocaine is the drug of choice in all wide-complex tachycardias of unknown origin.[6] Lidocaine is of no effect in supraventricular arrhythmias, and in fact, may even accelerate the ventricular response in patients with atrial fibrillation and the WPW syndrome.

It should be noted that since the advent of amiodarone there are a number of critical care units who prefer amiodarone to lidocaine in the treatment of multiple ventricular ectopics, VT and ventricular fibrillation.

Dosage

For multiple ventricular ectopics, sustained VT, symptomatic VT, as also for pulseless VT or refractory ventricular fibrillation, an initial bolus of 1–1.5 mg/kg body weight is given intravenously at a rate of 30–50 mg/minute. A maintenance drip with an infusion rate of 1–2 mg/minute generally suffices to prevent recurrence. A blood lidocaine level of 1.5–6 mg/mL is an effective suppressive range.

If the initial bolus is ineffective, two or more boluses of 1 mg/kg can be given at 5 minute intervals. Patients who require higher doses of the drug and higher plasma levels of lidocaine to revert to sinus rhythm, need a larger maintenance

dose of 2–4 mg/minute. A maintenance drip is generally continued for 24–48 hours. Doses should be reduced by 50% in patients with shock, heart failure or liver dysfunction and in patients older than 70 years.

Cardiac arrest victims may need only a single bolus of lidocaine. The drug can also be administered in patients with cardiac arrest through the endotracheal tube, using 2.5 times the intravenous dose. Once circulation has been restored after successful resuscitation from cardiac arrest, an intravenous infusion of 2 mg/minute of lidocaine should be given.

Adverse Effects

Side effects chiefly involve the central nervous system. These are dose-related effects, and are more frequently seen in the aged. Neurological toxicity includes dizziness, paresthesia, confusion, delirium, drowsiness and even coma. Seizures may also occur. Sinus node depression may occur. The drug is remarkably free of hemodynamic effects, but in large doses and particularly in old patients with poor LV function, the drug may further depress the myocardium, worsen failure and induce hypotension. Lidocaine can increase defibrillation thresholds and has been rarely reported to cause malignant hyperthermia.[7,8]

Quinidine[9-11]

This is a class I antiarrhythmic agent. It depresses depolarization and prolongs repolarization in the atria and the ventricles. It can facilitate atrioventricular (AV) conduction and prolongs the QT interval. Twenty percent of the drug is excreted by the kidneys, the remainder being metabolized by the liver. Plasma quinidine levels peak at about 90 minutes after oral administration of quinidine sulfate. Elimination half-life is 5–8 hours after oral administration. The drug dosage should be reduced in patients with hepatic or renal disease and in those with poor hepatic blood flow (e.g. in cardiac failure and shock).

Indications

Quinidine is a useful antiarrhythmic agent for suppressing supraventricular and ventricular ectopic activity and also for suppressing and reverting both atrial and ventricular sustained tachyrhythms. It does this chiefly by increasing the refractory period of the atria and ventricles and by suppressing atrial and ventricular ectopic activity. Prior to using quinidine for the conversion of atrial flutter or fibrillation to sinus rhythm, the ventricular rate should be first slowed by digitalis or verapamil or a beta blocker. This is because if quinidine is used first, it can slow the atrial flutter rate from 300 beats per minutes to 200 beats per minute. This effect coupled with enhanced AV conduction (a vagolytic effect of the drug) may convert a 2:1 AV response to a 1:1 response, with a resulting increase in the ventricular rate. The drug is no longer as freely used as before chiefly because of the danger of QT prolongation that could lead to torsade de pointes. It is also unavailable in India.

Dosage

For conversion of both sustained supraventricular and ventricular tachyarrhythmias, Quinidine is preferably used orally. The recommended dosage of 400 mg 2 hourly for 4–5 doses is preferred over 400 mg 6 hourly, as the former leads to a more frequent reversion to sinus rhythm. Quinidine can be given intravenously in an emergency situation, e.g. a VT not responding to lidocaine, amiodarone or direct current conversion. Quinidine gluconate is given in a dose of 10 mg/kg intravenously very slowly at a rate of 0.5 mg/kg per minute, the blood pressure and electrocardiogram (ECG) being constantly monitored.

Adverse Effects

The most common adverse effects include nausea, vomiting and diarrhea. CNS disturbances include hearing loss, tinnitus, visual disturbances, confusion, delirium and psychosis. Hypersensitivity responses include hemolytic anemia, thrombocytopenia, fever and rash. Remarkably enough, in our Indian patients these adverse effects are uncommon, the drug being fairly well tolerated. Its cardiovascular effects can indeed be dangerous and should therefore be very closely monitored. It can slow conduction and may produce a sinoatrial (SA) or AV block or a bundle branch block. Quinidine-induced cardiac toxicity can be treated with molar sodium lactate.

Quinidine may produce a QT prolongation and torsade de pointes, a polymorphic ventricular tachyarrhythmia which can cause a syncopal attack and may even be fatal. Syncope due to ventricular tachyrhythms is unrelated to plasma concentrations of quinidine or duration of therapy, though the majority suffer these episodes within the first 2–4 days. In these cases, the drug should be promptly omitted and hypokalemia, which is frequently present should be corrected. The drug of choice in a patient who has syncope from torsade de pointes is magnesium, given intravenously (2 g over 1–2 minutes followed by an infusion of 3–20 mg/minute).[12,13] Drugs that do not prolong the QT interval like lidocaine or phenytoin may also be tried. Atrial or ventricular pacing may act by suppressing depolarization. If pacing is not available, isoproterenol may be used. Quinidine may elevate serum digoxin levels by displacing digoxin from tissue receptors and by decreasing both its total body clearance and volume of distribution.

Procainamide[14]

This is an antiarrhythmic drug very similar to quinidine in its mode of action. It depresses depolarization and prolongs repolarization both in the atria and in the ventricles, facilitates AV conduction through its vagolytic effect and prolongs the QT interval. The drug is chiefly excreted through the kidneys, though it is also partly metabolized by the liver. About 15% is metabolized to N-acetyl procainamide, which also has antiarrhythmic effects and is excreted by the kidneys.

The drug's dosage should therefore be reduced in patients with a low-output state and in those with renal insufficiency. Renal clearance of procainamide is diminished by cimetidine.

Clinical Indications

The main indications for its use are: (1) emergency suppression of ventricular arrhythmias when amiodarone or lidocaine is ineffective, (2) conversion of atrial flutter or fibrillation after digitalis or verapamil or beta blockers have been first used to slow or block AV conduction.

Dosage

Most units in the West at one time used procainamide for the treatment of VT. Today lidocaine or amiodarone has replaced procainamide almost completely in the management of VT. Perhaps its use is in the occasional patient who fails to respond to lidocaine or amiodarone. We have stopped using procainamide for several years. Several intravenous regimes have been advocated. One regime is to give 25–50 mg of the drug intravenously over a 1 minute period. This is repeated every 5 minutes until the arrhythmia is controlled, or hypotension results, or the QT interval is prolonged by more than 50%. Another regime is to give a slow infusion of the drug at a rate of 2–6 mg/minute with a careful monitoring of the blood pressure and ECG. It is wise not to exceed a total dose of 1,000 mg. In less emergent situations, procainamide can be used orally—500 mg every 3–4 hours, the total daily dose being between 2 g and 4 g.

Adverse Effects

Hypotension, which can be precipitous, is the most frequent side effect. Procainamide is a myocardial depressant and can worsen myocardial function in a patient with LV disease. It can also induce ventricular arrhythmias by prolonging the QT interval. It can also suppress conduction in the SA node, or the AV node, or within the conduction system in the ventricles and can lead to various forms of heart block. The syndrome of systemic lupus erythematosus reported on prolonged oral administration of the drug does not occur following emergency administration of the drug. Procainamide should never be used to treat torsade de pointes associated with a prolonged QT interval.

Amiodarone[15,16]

This is a class III antiarrhythmic agent useful in the management of ventricular and supraventricular tachyrhythms in the ICU. It prolongs action potential duration and refractoriness: Though its main action is to block the potassium channel, it also blocks the sodium channel. It also prolongs the QT interval but is less likely to induce torsade de pointes than quinidine, procainamide or disopyramide. It also has a depressant action on the myocardium and can produce a mild alpha and beta blockade. The drug is lipid soluble and is metabolized by the liver. It is not excreted by the kidneys and the dose need not be reduced in patients with renal failure.

The onset of action after intravenous administration is generally within a few hours.[17] Oral medication takes 2–3 days or even 1–3 weeks to produce an effect and is therefore of no use in an emergency situation. Therapeutic serum levels range from 1 mg/mL to 3.5 mg/mL.

Clinical Indications

Amiodarone can suppress a wide range of supraventricular and ventricular tachyarrhythmias.[18] These include AV nodal reentrant tachycardia, junctional tachycardia, atrial flutter, atrial fibrillation, VT and ventricular fibrillation. Its efficacy is 60–80% for most supraventricular tachycardias (SVT) and 40–60% for VTs.[19] It has been shown to be superior to class I antiarrhythmic agents in maintaining sinus rhythm in patients with recurrent atrial fibrillation. In the ICU, this drug is used for VT resistant to lidocaine and in the management of supraventricular arrhythmias. Many units prefer amiodarone to lidocaine in the treatment of VT.

Dosage

A loading dose of 5 mg/kg dose is given intravenously over 20 minutes and is repeated after 30 minutes. This is then followed by a maintenance dose of 10 mg/kg per day for 3–4 days. One should do not exceed a total dose of 1.2 g in 24 hours. The drug is administered in a 5% dextrose infusion as it may precipitate in normal saline.

Adverse Effects

Amiodarone has significant potential toxicity. Cardiac side effects include bradycardia, hypotension, aggravation of tachyarrhythmias in 1–2%[20] and worsening of congestive heart failure in 2%. The drug can prolong the QT interval and should not be given to patients with torsade de pointes.

Noncardiac toxic effects chiefly involve the pulmonary and gastrointestinal (GI) systems. Pulmonary toxicity very rarely can begin acutely within 6–10 days of treatment in the ICU,[21] but generally occurs after a few months of continuous oral therapy. Acute lung toxicity, which can occur within 6 days of intravenous use of the drug, leads to a rapidly progressive interstitial lung disease that may not be reversible. Chronic toxicity is characterized clinically by cough, breathlessness and crackles over the lungs on auscultation. The underlying pathology consists of areas of pulmonary consolidation with progressive respiratory failure. The pathogenesis is believed to be related to an immune-mediated hypersensitivity response of the lung to the drug. Amiodarone should be promptly stopped at the first sign of lung involvement.

The drug can also produce liver cell dysfunction with elevated liver enzymes, GI disturbances and neurological dysfunction. Other potential toxic effects (e.g. corneal microdeposits and thyroid dysfunction) are not observed during use in critical care units. Prolonged use can cause hypothyroidism or rarely hyperthyroidism. A slate blue discoloration of the skin may be observed with chronic use. Patients are advised not to be exposed to bright sunlight

because of photosensitivity. Optic neuritis has been rarely observed, but the causal relationship with amiodarone has not been established.

In spite of its potential toxicity, the drug is indeed extremely useful in a critical care setting for a variety of supraventricular and ventricular arrhythmias.

As far as possible, amiodarone should not be used in combination with quinidine or procainamide as it increases the serum level of these drugs. If digoxin is being used, the dose should be reduced by 25–40%.

Dronedarone

Dronedarone is a new antiarrhythmic drug that is pharmacologically related to amiodarone, but lacks the iodine moiety that is associated with thyroid and pulmonary side effects. Dronedarone is given in a dose of 400 mg twice a day. Its chief use is in patients with paroxysmal atrial fibrillation (AF) maintaining both sinus rhythm and a slow rate successfully. When compared to amiodarone, dronedarone was associated with more recurrences of AF. It should be noted that the PALLAS trial showed that administration of dronedarone in patients with permanent AF was associated with an increase in the rates of heart failure hospitalization, stroke, and death.[22] This drug is contraindicated in: (1) elderly patients with asymptomatic permanent AF; (2) patients with severe LV systolic dysfunction or recent heart failure where it has been shown to increase total mortality.[23-25]

Esmolol[19,26]

Esmolol is a short-acting cardioselective beta blocker with a half-life of approximately 9 minutes after intravenous administration. It has an action similar to other beta blockers—it chiefly prolongs AV conduction, slows the heart rate and reduces contractility. The action starts within 2 minutes of an intravenous loading dose. It is metabolized by red blood cell esterases and is rapidly inactivated so that complete recovery from its physiological effects occurs within 20 minutes after intravenous administration. Its main indication is in the acute or emergency control of the ventricular rate in SVT, atrial flutter and atrial fibrillation.

Dosage

This drug is administered in a loading dose, an intravenous bolus of 500 mg/kg per minute being given over 1–2 minutes. A maintenance dose of 50–200 mg/kg per minute is then continued as a slow intravenous infusion.

Adverse Effects

These are the same as with other beta blockers, only these effects if present disappear within 15–20 minutes. The drug, therefore, has a higher margin of safety compared to other beta blockers, particularly in patients with LV dysfunction. Even so, hypotension, heart block, bronchospasm and acute heart failure may be observed.

Verapamil

Verapamil is a class IV antiarrhythmic agent that blocks the slow calcium channel in cardiac muscle.[26] It thereby reduces the plateau height of the action potential, shortens muscle action potential, and prolongs total Purkinje fiber action potential.[19] In vivo, verapamil prolongs conduction time through the AV node and lengthens functional and effective refractory periods of the AV node. Like all calcium channel blockers, the drug has a negative inotropic effect on ventricular contraction though this is not as marked as that observed with beta blockers. Verapamil also produces significant peripheral vasodilatation; the resulting hypotension induces reflex sympathetic stimulation. The drug produces coronary vasodilatation and decreases myocardial oxygen demand.

The drug acts promptly on intravenous administration. AV nodal conduction delay occurs within a few minutes and is detectable for over 6 hours. The elimination half-life of verapamil is 3–7 hours, 30% being metabolized in the liver, and 70% being excreted by the kidneys.[19]

Clinical Indications

The drug is extremely useful in the treatment of paroxysmal atrial tachycardia, AV nodal entry or reciprocating tachycardia. It should be tried if simple vagal maneuvers fail. However, most units prefer to administer intravenous adenosine as the drug of choice for the above mentioned supraventricular tachyrhythms. Even so, verapamil given intravenously terminates more than 90% of episodes of SVT. The drug is also used to slow the ventricular rate in atrial flutter and fibrillation. It can be used with digoxin for this purpose but should not be combined with beta blockers.

Verapamil has no action on and should not be used for VTs. As a general rule, intravenous verapamil should not be given in any wide QRS complex tachycardias. If the latter happens to be a VT, hemodynamic collapse (severe hypotension and arrest) may occur.

Dosage

For emergency use in critical care units, 5–10 mg is given intravenously over 2–3 minutes, with close monitoring of the blood pressure and ECG. Slowing of the ventricular rate in atrial fibrillation may be maintained if necessary, by the oral use of the drug, or by a continuous infusion of the drug at a rate of 0.005 mg/kg per minute.

Adverse Effects

Hypotension, during or immediately after intravenous administration, can be marked. This effect can be reversed by intravenous calcium gluconate. Because of its negative inotropic action, the drug can further depress cardiac function and cardiac output in a patient with LV dysfunction or in a patient with congestive cardiomyopathy. This adverse effect can be dangerous and at times fatal if the drug is administered to a patient already on beta blockers.[27] Bradycardia, AV block

and asystole can also occur as dangerous side effects; they are more likely to occur when the drug is combined with beta blockers.

Contraindications to the use of verapamil are sinus node dysfunction, AV block without a pacemaker in place, atrial fibrillation occurring against the background of a WPW syndrome with antegrade conduction over an accessory pathway. In the latter situation, verapamil can facilitate conduction through the accessory pathway with a marked rise in ventricular rate that may end with VF and death. The drug is also contraindicated in VTs, all wide QRS complex tachycardias, in hypotensive states and in cardiogenic shock. It is generally contraindicated, as stated earlier, in a patient receiving beta blockers. Verapamil can decrease the excretion of digoxin by 30%; the dose of the latter should therefore be reduced, if it is to be used with verapamil.

Diltiazem

The mechanism of action of diltiazem is the same as verapamil. Intravenous diltiazem is effective in terminating paroxysmal supraventricular tachycardia (PSVT) and in controlling the ventricular rate in patients with atrial flutter and fibrillation. Diltiazem should not be used for VT.

Dosage

An initial bolus of 0.25 mg/kg (20 mg in an average adult) is administered intravenously over 2 minutes. If satisfactory rate control in atrial flutter or fibrillation is not achieved, a further 20 mg is given over 2–3 minutes after a lapse of 15 minutes. The bolus dose is followed by an infusion at 5–15 mg/hour. The infusion should not exceed a period of 24 hours.

Adverse Effects

Adverse effects are as those that are observed with verapamil. The hypotensive and negative inotropic effects are however much less marked as compared to verapamil. Verapamil and diltiazem are best avoided in patients with a sick sinus syndrome or AV block in the absence of a functioning pacemaker.

Adenosine

This is a comparatively new drug used to treat SVT.[28,29] It is administered intravenously and is an extremely effective antiarrhythmic agent. Adenosine interacts with A_1 receptors present on the extracellular surface of cardiac cells and activates K^+ channels. The increase in K^+ conductance shortens the atrial action potential duration, hyperpolarizes the membrane potential and decreases atrial contractility.[19] It delays conduction and induces a block in the AV node. Adenosine is removed from the system by washout, by enzymatic degradation to inosine, phosphorylation to adenosine monophosphate or by re-uptake into the cells.[19] It has a very short elimination half-life of 1–6 seconds. It is worth noting that therapeutic concentrations of theophylline block the action of adenosine. Dipyridamole blocks re-uptake of adenosine and delays its clearance from the circulation; hence, smaller doses of adenosine must be used in patients on dipyridamole. The onset of action of adenosine begins in less than 30 seconds and lasts for 1–2 minutes.

Clinical Use

This drug is used by many as the first choice to terminate acutely occurring SVT such as AV nodal or AV re-entry tachycardias.[30-32] It is particularly indicated when SVT occurs in patients with heart failure, hypotension, WPW syndrome or in patients receiving calcium channel blockers or beta blockers.

Dosage

An intravenous dose of 6 mg is given by a rapid intravenous injection. After 2 minutes, a second dose of 10 mg may be administered in the same manner, if necessary. The dose should be reduced by 50% if the injection is given through a central line or in patients on beta blockers, calcium channel blockers or dipyridamole (see Chapter Tachyarrhythmias in the Intensive Care Unit). Conversion to sinus rhythm occurs in 90–100% of cases.

Adverse Effects

Facial flushing, dizziness, nausea, dyspnea and angina-like chest pain are observed quite frequently. Sinus bradycardia or a temporary AV block may occur. Cardiac asystole for a few seconds may be a worrying feature.

Digoxin

Digoxin is still very frequently used in the ICU both in the management of cardiac failure and in the control of supraventricular arrhythmias.

Digitalis has a significant inotropic action on the heart. It binds to and inhibits Na^+ K^+ adenosine triphosphatase (ATPase) resulting in an increased intracellular Na^+, which is exchanged for extracellular calcium.[33] The increased availability of activated calcium to the contractile proteins of the myocardial cells results in enhanced contractility. The action of digoxin on Na^+ K^+ ATPase activity also alters the transmembrane potential of other cells affecting the refractory period, conduction velocity and excitability. Various cell types may be affected differently accounting for different effects on the atria, on the AV node and conducting tissues and on the ventricles. Digitalis (including digoxin) enhances the parasympathetic, and diminishes the sympathetic effects on the heart. It also acts as a peripheral vasoconstrictor.[34]

The main action of digitalis glycosides in clinical practice is an inotropic action on the heart and a prolongation of AV conduction. The latter is due to varying degrees of block in the AV node. This effect is made use of in slowing the ventricular rate in atrial flutter and fibrillation and in inhibiting re-entrant SVT.

Pharmacokinetics

Digoxin is widely distributed in the tissues and the serum half-life is fairly long (36–48 hours). Intravenous digoxin acts within 1–2 hours of administration. Therapeutic blood levels of digoxin are between 0.8 ng/mL and 2 ng/mL. Unfortunately, the drug has a relatively narrow therapeutic ratio, and toxicity may occur even when serum levels are within the therapeutic range. The drug is primarily cleared by the kidneys. Interactions between digoxin and other drugs are frequent. Impaired renal function and drug interactions, which raise serum digoxin levels dangerously, contribute to the frequent occurrence of digitalis toxicity observed in the ICU.

Clinical Indications

These chiefly include: (1) cardiac failure—both LV failure and congestive cardiac failure; (2) supraventricular tachyarrhythmias—atrial flutter, atrial fibrillation and re-entrant SVT.

Dosage

Emergency slowing of the ventricular rate in supraventricular tachyrhythms, or a quick inotropic action in LV failure, necessitates intravenous administration of the drug. 0.25 mg (or in exceptional instances 0.5 mg) is given intravenously over 5 minutes. 0.25 mg is then repeated 4–6 hourly till a digitalizing dose of 0.75–1 mg is reached over a 24 hour period. It is wise not to exceed this dose, at least not in patients in our country. Patients with atrial flutter or fibrillation may require a larger dose of 1.5 or even 1.75 mg in 24 hours. A maintenance dose of 0.25 mg orally daily for 5–6 days in a week generally suffices. In the presence of renal failure, the loading and maintenance doses need to be sharply reduced. Frequent digoxin levels may need to be done and digoxin levels should be kept below 2.0 ng/mL. In the elderly, intravenous digoxin should be given with caution. We prefer to give half the loading dose followed by a maintenance dose of 0.125 mg orally daily for 5 days in a week.

Toxic Effects

Digitalis is a toxic proarrhythmic drug particularly in the presence of hypokalemia, hypomagnesemia and renal insufficiency. The simultaneous use of quinidine alters the renal clearance and the volume of distribution of digoxin. In fact, therapeutic levels of quinidine may nearly double the serum concentration of digoxin. The dose of digoxin should be halved when using quinidine. Amiodarone and verapamil have similar but lesser effects on digoxin levels in the blood.

Digitalis-induced arrhythmias and their management have been discussed in an earlier chapter. Nausea, vomiting, and visual disturbances (colored vision) are also observed in patients in the ICU and may precede or accompany rhythm disturbances caused by digoxin. Digoxin is contraindicated in the presence of AV block, in severe hypokalemia or hyponatremia, and in hypertrophic cardiomyopathy.

NEWER ANTIARRHYTHMIC AGENTS[5,35]

Newer Class IC Antiarrhythmic Drugs

Flecainide and propafenone are class IC antiarrhythmic agents used to treat ventricular tachyarrhythmias. The main risk associated with their use is the precipitation of life-threatening ventricular arrhythmias. These drugs can suppress the sinus node and impair AV and infra-nodal conduction in patients with conduction disease. They also depress systolic LV function. Flecainide is given at 50–200 mg orally twice a day; many elderly patients only require 50 mg twice a day. The starting dose of propafenone is 150 mg every 8–12 hours.

It is of interest to note that ventricular premature beats were believed to lead or rather predict sudden cardiac death in patients with myocardial infarction who developed a cardiomyopathy. The CAST study was designed to assess the impact suppression of these ectopic beats in this high-risk population.[36,37] It was observed that patients, who received the above newly introduced antiarrhythmic agents, had a 2.5-fold higher mortality than patients in the control arm of the trial forcing the premature termination of this study.

Newer Class III Antiarrhythmic Drugs

Sotalol is a nonspecific beta adrenergic receptor blocker with potassium channel blocking properties. It is used in the treatment of ventricular arrhythmias and atrial fibrillation. Oral dosing is usually 80–160 mg twice a day. The most dangerous side effect is a prolongation of the QT interval that can lead to torsade de pointes. The drug can aggravate airways obstruction in patients with asthma or chronic obstructive pulmonary disease.

Ibutilide is a short-acting potassium channel blocker given intravenously for the quick termination of atrial fibrillation or flutter. Ibutilide is given as an intravenous bolus in a dose of 1 mg over 10 minutes or until conversion, whichever occurs first. The major side effect is precipitation of sustained ventricular arrhythmias. The patient should be monitored in the ICU continuously with resuscitative equipment at hand.

Dofetilide is another class III antiarrhythmic drug excreted by the kidneys. The dosage is determined by creatinine clearance (CrCl) and adjusted according to changes in the corrected QT (QTc) interval. Initial dose of dofetilide is 500 µg twice a day if the CrCl is more than 60 mL/minute, 250 µg twice a day if the CrCl is 40–60 mL/minute and 125 µg twice a day if the CrCl is 20–40 mL/minute. It has been found safe in patients with cardiomyopathy. The dosage needs careful adjustment with continuous patient monitoring.

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CHAPTER 26

Hypertensive Emergencies and Aortic Dissection in the ICU

HYPERTENSIVE EMERGENCIES

INTRODUCTION

The incidence of hypertension is increasing globally. Population data suggest that 97.2 million individuals worldwide have hypertension[1] and 30% of hypertensive individuals are unaware of this diagnosis. This chapter first briefly introduces the concept of hypertensive urgency and then focuses on hypertensive emergencies, also termed hypertensive crisis.

Hypertension can exist without evident acute or chronic target organ dysfunction. Hypertensive urgency is characterized by an elevated blood pressure (BP), systolic often greater than 180 mm Hg, diastolic greater than 115 mm Hg without evidence of any acute end-organ damage. Hypertensive urgency may be associated with chronic stable complications such as renal insufficiency, ischemic heart disease (IHD) [stable angina, past history of myocardial infarction (MI)], and/or cerebrovascular disease in the form of a history of past transient ischemic episodes or a past history of a cerebrovascular accident. There is no threat of an immediate, impending acute insult. Hypertensive urgency may be the result of improper treatment or lack of compliance.

Hypertensive emergency, also called hypertensive crisis, is defined as an acutely elevated BP associated with acute end-organ damage. The organs chiefly involved are the kidneys, the heart and the central nervous system (CNS). Unless properly treated there is a significant morbidity and mortality attached to this emergency within an immediate short span of time. The evolution of a hypertensive crisis is dependent both on the degree of rise in BP and the time course over which this BP has risen. In patients who are previously hypertensive, the blood pressure in an acute crisis may well be greater than 210 mm Hg systolic and greater than 120–130 mm Hg diastolic. In previously normotensive individuals, as, also in pregnant females and in children, hypertensive crisis may occur with a comparatively lesser or even minor increase in BP.

PATHOPHYSIOLOGY OF HYPERTENSIVE CRISIS

A sudden sharp increase in the BP is the initiating feature that transforms simple hypertension to an acute hypertensive crisis. BP is the product of the cardiac output and peripheral resistance. The initial sharp rise in BP is due to a sharp increase in vascular tone with a corresponding increase in peripheral vascular resistance. There is evidence to suggest that the sharp increase in BP leads to increased mechanical stress on the arteriolar wall with a disruption of endothelial integrity.[2] Disruption of endothelial integrity results in diffuse microvascular lesions, characterized by a fibrinoid necrosis of the arteriolar walls, a consistent histological feature of hypertensive crisis.[3,4] Other factors may well contribute to the evolution of an acute hypertensive crisis. Increase in peripheral vascular resistance occurs in part from activation of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II may activate genes for the proinflammatory cytokine interleukin and nuclear factor κB thereby directly injuring the vessel wall.[5,6] Hormones such as catecholamines, vasopressin, endothelin and immunological factors may also contribute to the increase in vascular tone. The end result of

these peripheral vascular changes is ischemia to vital organs such as the brain, kidney and the heart.

CRITICAL CARE IN HYPERTENSIVE EMERGENCIES

Hypertensive emergencies invariably need critical care. The danger caused by a sudden rise in BP to high levels is related as already stated to disturbance in structure and function of important organ systems. Equally important is the potential hazard of a sudden increase in BP in specific critical situations such as in the perioperative or immediate postoperative phases of intracranial surgery, open heart surgery or other vascular surgeries. Thus, a sudden rise of BP during or after intracranial surgery or following trauma to the head is fraught with risk of increasing cerebral edema with all its attendant complications. A hypertensive crisis, perioperative or postoperative following open heart surgery, subjects the heart to an unnecessary increase in afterload and can trigger cardiac failure and pulmonary edema. A rise in BP in the immediate post-coronary artery bypass graft (CABG) phase can also accentuate myocardial ischemia and can precipitate MI. The risk of increased bleeding due to postoperative hypertension is also ever present, particularly following open heart surgery and vascular surgery.

Patients with hypertensive crisis needing critical care can be grouped as follows—

- An acute hypertensive crisis causing acute structural damage and functional changes in the following major organ systems—
  - *Central Nervous System—problems involving the CNS* include hypertensive encephalopathy, cerebral hemorrhage, subarachnoid hemorrhage, cerebral *infarction*, stroke-in-evolution.
  - Cardiovascular System—acute hypertensive crisis can precipitate unstable angina (UA), MI, acute left ventricular failure, congestive heart failure, aortic dissection.
  - Renal System—malignant hypertension with rapidly evolving renal destruction and failure are the most dreaded features of severe accelerated hypertension.
- Hypertensive crisis posing a potential hazard in specific critical situations—
  - After intracranial surgery (greater risk of cerebral edema and bleeding).
  - After trauma to head—again, a greater risk of cerebral edema and bleeding.
  - After open heart surgery (risk of MI, acute heart failure, bleeding).
  - After vascular surgery (risk of bleeding).
  - After other major surgery (risk of bleeding, risk to sutures).
- Eclampsia—this is a special situation in pregnancy when sudden increase in BP is associated with seizures and albuminuria. There is a great risk of multiorgan failure particularly involving the CNS and kidneys.
- Uncommon conditions causing a sudden dangerous rise in BP—
  - Pheochromocytoma often causes paroxysmal hypertension. Even so, the commonest cause of paroxysmal hypertension in clinical practice, occurs against a background of mild to moderate essential hypertension.
  - Drug reactions in patients on monoamine oxidase (MAO) inhibitors.
  - Rare instances in our country of acute hypertension in cocaine addicts and in lead poisoning and encephalopathy.
  - Sudden withdrawal for whatever reason of potent antihypertensive drugs.

APPROACH TO HYPERTENSIVE EMERGENCIES

Hypertension from any cause can be complicated by an evolution into an acute crisis. The commonest cause of an acute hypertensive crisis is essential hypertension. Hypertensive emergencies can also occur in secondary hypertension and in individuals who give no history of hypertension, as in pheochromocytoma, acute glomerulonephritis, toxemia of pregnancy and eclampsia. Cocaine addicts are also known to present with an acute hypertensive crisis.

An important feature in the history is to determine whether the patient has had a background of hypertension and if so, the duration of the hypertension. If there is a history of long standing hypertension then the underlying etiology is generally essential hypertension. The possible factors precipitating an acute crisis in a patient need to be carefully evaluated. Emotional stress, physical fatigue, excessive ingestion of salt, administration of corticosteroids or the occurrence of secondary renovascular problems are important causes of an acute crisis in some patients. Not uncommonly no underlying triggering factors can be found for a precipitous rise in BP.

The management of a hypertensive emergency rests on quick assessment and immediate treatment. Quick assessment consists of a relevant history and physical examination. The urgency of the situation at times may demand measures to control the hypertensive crisis as the first and initial step.

Patients with hypertensive emergency present with a variety of symptoms, the most common being headache. It is usually sudden in onset, located in the occipital or frontotemporal region. Symptoms may relate to the CNS and include disturbances in vision, transient ischemic attacks, stroke, stroke-in-evolution, confusion, drowsiness and seizures. Symptoms related to the cardiovascular system (CVS) include cardiac pain and breathlessness and to the renal system include nocturia, polyuria, and hematuria. Nausea and vomiting frequently occur with an acute rise in BP, as in patients presenting with hypertensive encephalopathy. The physical examination in an acute emergency should be brief and is conditioned to an extent by the nature of the presenting illness. BP should be measured in both arms; the diastolic BP

in an acute crisis is generally greater than 120 mm Hg. A point of note is that calcification of the vessel walls may prevent compression of the vessel wall by the BP cuff, so that in these patients there appears to be a pseudo or false increase in the BP. Pseudo-hypertension can occur with severe atherosclerosis, Monckeberg's medial calcification and metastatic calcification occurring in some patients with end stage renal disease. The arteries in these instances are thick, almost hard when palpated. A palpable radial artery after proximal compression of the vessel (Osler's maneuver) suggests this diagnosis.

Examination of the CVS should include evidence for left ventricular hypertrophy (seen in long standing hypertension), evidence of left ventricular failure (a diastolic gallop with basal crackles) and the presence or absence of a carotid bruit. All major pulses should always be palpated for evidence of any inequality.

A brief CNS examination should include a rapid assessment of cognition and memory, of motor function, of focal signs and of the tendon and plantar reflexes. A fundus examination is mandatory as it reveals the severity of hypertension (presence of exudates and hemorrhages), the duration of hypertension [sclerotic vessels with arteriovenous (A-V) nicking] and the presence of malignant hypertension as judged by papilledema.

Examination of the abdomen should include careful palpation for enlarged ballotable kidneys as is observed in polycystic kidneys and for clinical evidence of an aortic aneurysm.

It is important to assess priorities in management. Though control of hypertension is of vital importance, the presence of continuous seizures should prompt the urgent use of antiepileptic drugs. Similarly, the use of aspirin or anticoagulants in a patient with a stroke or stroke in evolution should be delayed till such time as imaging studies have excluded an intracerebral hemorrhage.

Emergency laboratory investigations are often of marginal help. A routine blood count, erythrocyte sedimentation rate (ESR) and urine examination are necessary. The urine often shows mild proteinuria, red blood cells and occasional casts. Gross proteinuria points to glomerulonephritis. Serum electrolytes, serum bicarbonate, serum creatinine, prothrombin time, activated partial thromboplastin time (PTT), a pregnancy test when appropriate, toxicological screening of urine and blood (especially for lead and cocaine) also when appropriate, may be necessary.

A chest X-ray and electrocardiogram (ECG) will help further assess cardiac function in relation to a hypertensive crisis. Evidence of frank cardiac failure should warn the intensivist against the use of a beta-blocker. Special imaging tests include a magnetic resonance imaging (MRI) for CNS lesions and for possible aortic dissection. Ultrasonography (USG) of the abdomen will determine kidney size and detect an aortic aneurysm. Echocardiography is of use in assessing wall motion abnormalities, ejection fraction and the presence of clots within the heart. There should be a protocol, which allows a sequential work-up based on immediate priorities; these would depend on the nature of the crisis and the presenting features.

MANAGEMENT OF HYPERTENSIVE EMERGENCIES

Patients with an acute hypertensive crisis often have BP greater than 220 mm Hg systolic and greater than 120–130 mm Hg diastolic. They are treated in an intensive care unit with monitoring of the BP by arterial cannulation or through the use of automated cuff measurements. Invariably in an acute crisis, drugs should be used parenterally to reduce the BP. Marked fall in the BP should be avoided. In many cases, it may be unwise or even harmful to reduce the BP to normal levels for fear of a sharp reduction in the coronary, cerebral and renal circulation. The speed at which BP should be reduced depends on the nature of the emergency or crisis.

In most but not all clinical situations, the BP is reduced by 20–25% in the first 15 minutes–2 hours.[7] Once the BP is stabilized at this level, it is further reduced to 160/100 mm Hg over the next 3–6 hours. If the patient is known to have been normotensive before the acute crisis, the blood pressure could be brought down to normal levels over the next 24–48 hours. Otherwise, if the patient is a known hypertensive, it is prudent to allow the BP at 140–150/90–100 mm Hg. The method of reduction described above allows CNS blood flow autoregulation to be generally well maintained.

There are however clinical situations, which require special consideration—

- In ischemic cerebral infarction or a stroke-in-evolution the BP should not be reduced unless it is above 220/120 mm Hg or the patient is a fit candidate for thrombolytic therapy.
- In patients with carotid artery stenosis, a past history of IHD, or of a cerebrovascular accident, or in patients with established chronic renal insufficiency, the BP should be brought down even more gradually than stated earlier.
- Fulminant pulmonary edema due to acute left ventricular failure may require a more rapid reduction in BP. The same directive applies to patients with active severe UA and patients in acute congestive cardiac failure.
- Hypertensive encephalopathy characterized by seizures, or mental obtundation, or coma due to cerebral edema requires an urgent more rapid reduction of BP.
- Acute dissection of the aorta is one condition which requires a very rapid reduction of the blood pressure to preferably 100 mm Hg systolic, within a period of 15–30 minutes.

Drugs Used in Hypertensive Crisis[8]

The drugs used parenterally to treat hypertensive crisis are—

- Intravenous (IV) nitroglycerin and IV nitroprusside, which act as vasodilators.
- IV labetalol, which is an α and β adrenergic blocker.
- IV nicardipine, a calcium channel blocker.
- Esmolol given IV as a short acting β_1 antagonist.
- IV enalapril, an angiotensin-converting-enzyme (ACE) inhibitor.

- Phentolamine, which is an α adrenergic blocker, chiefly used to counter an acute hypertensive crisis caused by a pheochromocytoma.
- Fenoldopam, which is a strong dopa agonist and which lowers BP by decreasing peripheral vascular resistance. We have no experience with this drug.
- Nifedipine sublingually (squeezed from a punctured capsule) is the only non-parenteral drug that can sharply reduce BP.[8] It is best not to use more than 5 mg sublingually as the fall in BP though temporary may be dramatic and uncontrolled. Though anecdotal reports of MI and arrhythmias have been reported following sublingual nifedipine, we have never encountered problems when the drug is used in the dose stated above.

The dosage, use, adverse effects of drugs in parenteral use have been summarized in Table 1.

Once a marked increase in BP is controlled by IV therapy, oral therapy using an appropriate single drug or a combination of drugs is given to maintain control. A careful transition from IV to oral medication is desirable. Calcium channel blockers, labetalol, beta-blockers, ACE inhibitors are commonly used oral preparations given singly or in combination. In fact, when the emergency is not very acute, and the BP is not unduly raised, oral medication (which should exert BP control over 12–24 hours) may be preferred to parenteral medication.

The ideal parenteral drug should be quick acting, effective and rapidly reversible, should not exhibit tachyphylaxis and should have minimal sideeffects on other organ systems. No drug fulfills all these criteria ideally. The quickest way to bring the BP down sharply is the use of IV nitroprusside, which acts through a direct vasodilator action on the arteriolar, capillary

Table 1: Parenteral drugs used in the management of hypertensive crisis

Drugs	*Dose*	*Onset of action*	*Duration of action*	*Adverse effects*
Drugs with Rapid Action				
Sodium nitroprusside	0.25–10 µg/kg/min as IV infusion	Immediate	1–3 minutes	Hypotension, nausea, vomiting, muscle twitchings, cyanide poisoning with prolonged excessive use
Nitroglycerine	5–100 µg/min as IV infusion	2–5 minutes	1–3 minutes	Tachycardia, headache, flushing, vomiting, methemoglobinemia
Diazoxide	50 mg IV bolus repeated at 5–10 minutes intervals, or 15–30 mg/min IV infusion	1–2 minutes	6–8 hours	Hypotension, fluid retention hyperglycemia, tachycardia
Hydralazine	10–20 mg IV 10–50 mg IM	1–20 minutes 20–30 minutes	3–6 hours	Tachycardia, flushing, headache, vomiting, precipitation of angina
Phentolamine	5–15 mg IV	1–2 minutes	10–30 minutes	Tachycardia, flushing
Trimethaphan	1–4 mg/min IV infusion	1–5 minutes	5–10 minutes	Orthostatic hypotension, bowel or bladder paresis, blurred vision, dry mouth
Esmolol	500 µg/kg/min for 4 minutes; then 150–300 µg/kg/min IV	1–2 minutes	8–10 minutes	Hypotension
Labetalol	20–80 mg IV bolus every 10 minutes 2 mg/min IV infusion	5–10 minutes	3–6 hours	Vomiting, dizziness, nausea, postural hypotension, precipitation of cardiac failure
Propranolol	1–5 mg IV bolus; 3 mg/hour IV infusion	1–2 minutes	3–6 hours	Bronchospasm, hypotension
Nicardipine hydrochloride	5–15 mg/hour as a loading infusion; 3–8 mg/hour as a maintenance infusion IV	1–3 minutes	15–40 minutes	Hypotension, headache, flushing
Enalaprilat	0.625–1.25 mg IV bolus every 6 hours	10–15 minutes	6–8 hours	Hypotension, cough, hyperkalemia, renal insufficiency
Slower Acting Drugs				
Reserpine	1 mg IV; 2–2.5 mg repeated after 4–6 hours	2–4 hours	Few weeks	Drowsiness, Parkinsonian-like rigidity, reactivation of peptic ulcer, nasal obstruction, bronchospasm
Alpha methyldopa	250–500 mg IV 6 hourly	1–3 hours	90–120 minutes	Drowsiness

and venous walls. The drug is potentially dangerous and therefore merits a more detailed description of its use. Its prime use is in patients with hypertensive encephalopathy where the BP may be greater than 250/130 mm Hg. A number of patients in our experience are extremely sensitive to this drug. It should always be given through a microdrip starting with 0.25 ug/kg per minute. A 60 kg patient would receive 15 ug/minute which would work out to 8–9 microdrops/minute. The BP should be continuously monitored preferably through cannulation of the radial artery. If necessary, one can increase the flow rate by five microdrops at 3–4 minutes interval. The blood pressure can occasionally crash to unrecordable levels. Fortunately, the effect of the drug is short lived, so that the BP starts to rise within a few minutes of stopping the drug. If severe hypotension does not quickly and spontaneous recover a titrated dose of noradrenaline is given in a separate infusion.

The drug today is not as frequently used as before for fear of causing sudden severe hypotension and for fear of cyanide poisoning (suspected when the serum lactate is raised and when there is a fall in pH) and thiocyanate toxicity. It is best not to use the drug for more than 48 or at most 72 hours.

Preparation 50 mg of the drug is added to 500 mL of 5% dextrose, so that 1 mL (60 microdrops) of this constituted solution contains 100 ug. The solution should be protected from light by wrapping it in a dark cloth. It should be freshly prepared and promptly used. Normally it is faint brown in color and should not be used if the color changes to dark brown.

Treatment Recommendations in Hypertensive Crisis Based on Etiology

Cerebral Infarction

Studies show that the areas surrounding the infarcted region are ischemic but potentially can be restored to function if reperfused. This is referred to as the ischemic penumbra. Also, in an acute cerebral infarct autoregulation is impaired and cerebral blood flow is not preserved in a predictable manner. Acute reduction of BP in these circumstances could potentially increase the area of infarct with unfortunate clinical consequences.

The current recommendations[9] are—

- To refrain from reducing the BP in an acute cerebral infarct except when the systolic BP is over 220 mm Hg and diastolic greater than 120 mm Hg. The pressure in the above circumstance is reduced by 15–25% over 24 hours.
- In patients who are considered appropriate for thrombolytic therapy, the BP must be reduced to less than 185 mm Hg systolic and less than 110 mm Hg diastolic.

Subarachnoid Hemorrhage[10]

Untreated severe hypertension can be dangerous. The recommendation is to reduce the hypertension by 20–25% over the first 6–12 hours but not less than 160–180/100 mm Hg.[10] Labetalol is the preferred agent as there are no adverse effects on the intracranial pressure or cerebral perfusion pressure. Oral nimidopine within 4 days of the acute event is believed to decrease vasospasm and cerebral ischemia. IV nitroglycerine or IV nitroprusside are not usually first line drugs as they could cause a further increase in cerebral volume and intracranial pressure because of their vasodilator effect.

Intracranial Hemorrhage

A recent consensus[11] states that—

- The blood pressure should be lowered by IV medication when the systolic BP is greater than 200 mm Hg or the mean arterial pressure (MAP) greater than 150 mm Hg.
- If intracranial hypertension is suspected, aggressive lowering of BP with continuous or intermittent IV medication is to be considered when the systolic BP is greater than 180 mm Hg or the MAP greater than 130 mm Hg.
- If there is no suspicion of increased intracranial pressure and the systolic BP is greater than 180 mm Hg and the MAP greater than 130 mm Hg, the BP should be lowered to a level of 160/90 mm Hg or a MAP of 110 mm Hg.

There is no consensus on the antihypertensive agent of choice. Labetalol is often used, though it may lead to worsening bradycardia. Vasodilator therapy is also often used in the presence of increased intracranial pressure. These patients have high circulatory catecholamines in the blood. If vasodilators are not effective, a beta-blocker is given in addition. An ACE inhibitor IV enalaprilat is also a good choice to control the BP. Once the sharp increase in BP is brought under control, oral medication in the form of a calcium channel blocker or an ACE inhibitor or labetalol singly or in combination can be given to maintain control.

Cerebral Trauma

In most trauma centers intracranial pressure monitoring has become a necessary standard of care. Current recommendations are to maintain a cerebral perfusion pressure of 70 mm Hg and a MAP above 90 mm Hg. When choosing an antihypertensive drug, a major consideration is its effect on intracranial pressure. A combination alpha- and beta-blocker (labetalol) or nicardipine may be preferred when there is increased intracranial pressure.[12] In the absence of intracranial hypertension vasodilators may be preferred.

Use of antihypertensives in malignant hypertension and hypertensive encephalopathy is given under the separate description of these entities.

MALIGNANT HYPERTENSION

Malignant hypertension is characterized by severe hypertension with hypertensive neuroretinopathy. The fundus examination classically shows flame shaped hemorrhages, cotton-wool exudates and papilledema. Some patients may just show severe papilledema. This syndrome is associated with nephropathy progressing to renal failure, microangiopathic hemolytic anemia and cardiac failure. Critical care is often needed in the presence of rapidly deteriorating

renal function, cerebrovascular accident or cardiac failure. Malignant phase hypertension is invariably associated with a marked increase in renin activity even when the underlying hypertension is essential.

The objective is to treat severe hypertension aggressively in order to prevent increasing ischemic end-organ damage. To protect cerebral function, the BP should be reduced by about 20% in the first hour and then further reduced to 160/100 mm Hg over the next 8–12 hours. The urine output, cerebral, renal and cardiac functions need careful monitoring. Nitroprusside in an IV infusion is often used to achieve this objective. Many patients are exquisitely sensitive to this drug, so that the drug to start with should be infused at not more than 5 μg/minute and titrated further to achieve BP control. Alternatives to nitroprusside are labetalol, nicardipine, fenoldopam. A gradual transition to oral drugs can be made once BP control is achieved.

It is not uncommon for renal function to deteriorate even further once the BP is controlled. Renal function, however, generally starts to improve after a period of 2 months; recovery at times is possible even after 1–2 years. In the interim period, some patients may require dialysis, particularly when the serum creatinine rises to greater than 4.5 mEq/L. Recovery of renal function is more likely to occur when on USG the combined length of both kidneys is greater than or equal to 20 cm and less likely if the combined length is less than or equal to 14 cm. Unfortunately, a number of patients progress to end-stage renal failure, requiring permanent dialysis even when the BP is controlled. This is particularly so when the underlying cause of malignant hypertension is chronic glomerulonephritis.

Relatively asymptomatic patients with malignant hypertension may present just with neuroretinopathy. The BP in these individuals can often be controlled by oral medication. Calcium channel antagonists are safe. ACE inhibitors can be used with caution, guarding against hyperkalemia, particularly in patients with renal insufficiency.

HYPERTENSIVE ENCEPHALOPATHY

Hypertensive crisis may manifest as hypertensive encephalopathy, a dangerous yet reversible condition, if promptly and appropriately treated.

In hypertensive encephalopathy the MAP exceeds the limits of autoregulation, so that edema of the brain results from extravasation of fluid and plasma proteins. The clinicopathological entity that ensues is termed reversible posterior leukoencephalopathy, a condition caused by vasogenic subcortical edema without infarction.

It is to be noted that hypertensive encephalopathy is just one of the many other medical conditions that can result in reversible posterior leukoencephalopathy.[13]

Clinical Features

The clinical features consist of severe headache, drowsiness, obtundation, visual disturbances, including an inability to see, mental confusion, speech disturbances, and most important of all, seizures. The latter may be the sole presentation of this disorder. Focal signs are generally absent unless there has been an intracerebral bleed. However, papilledema is invariably present; its absence should raise doubts on the diagnosis.

Box 1: Differential diagnosis of hypertensive encephalopathy

- Intracerebral or subarachnoid hemorrhage
- Cerebral infarction
- Subdural hematoma
- Mass lesion (e.g. trauma)
- Seizure disorder
- CNS vasculitis
- Drug poisoning

The condition is completely reversible within 24–48 hours, if the BP is appropriately controlled, in contrast to the persistence of obtundation, mental confusion observed in an intracerebral bleed. The syndrome generally occurs against a background of severe hypertension but even a modest elevation of BP can lead to encephalopathy in children, particularly against the background of glomerulonephritis.

Among routine investigations, imaging of the brain is vital to exclude an intracranial hemorrhage, subarachnoid hemorrhage or a massive cerebral infarct. An MRI of the head in hypertensive encephalopathy reveals edema in the occipital and parietal lobes (posterior leukoencephalopathy); edema in other regions of the cerebral hemispheres and occasionally brainstem involvement may also be observed.

Treatment consists in appropriately lowering the BP in the clinical setting of cerebral edema and ischemia. The MAP should initially reduced by 20% in the first 2 hours and further reduced to 150/100 mm Hg over the next 4–6 hours. The diagnostic feature of hypertensive encephalopathy is complete recovery within 12–24 hours of reduction of BP. If hypertensive encephalopathy is untreated or inappropriately treated, coma and death may result.

The differential diagnosis of hypertensive encephalopathy is given in Box 1.

HYPERTENSIVE CRISIS IN ECLAMPSIA[14]

The diagnosis of eclampsia requires the presence of seizures, edema, proteinuria and hypertension in pregnancy. An MRI of the head shows edema within the occipital and parietal lobes (posterior reversible encephalopathy syndrome or posterior leukoencephalopathy). This resolves with successful treatment of the disorder. Eclampsia should be differentiated from toxemia of pregnancy (pre-eclampsia), wherein seizures are absent and where a prompt reduction in BP may well prevent morbidity and transition to eclampsia. The antihypertensives best suited to the pregnant state include hydrazaline and alpha methyldopa. Between 10–40 mg hydrazaline is best given orally or intravenously every 6 hours. Alpha methyldopa is given in a dose 500 mg four times a day. Calcium channel blockers can be added to this regime if necessary.

Magnesium sulfate administered intravenously is extremely useful for control of seizures. It also has an antihypertensive effect. A loading dose of 4–6 g is given intravenously over 20–30 minutes. This is followed by 1.5–3 gm/hour given intravenously. A plasma magnesium level of 4–6 mEq/L is considered to be within the therapeutic range. Once seizures and hypertension are reasonably controlled, the fetus should promptly be delivered.

PERIOPERATIVE AND POSTOPERATIVE HYPERTENSION

Some hypertensive patients, ordinarily well controlled, may develop a sharp rise in BP just before surgery. Elective surgery is preferably postponed till the BP again settles. If postponement is not possible, BP should be reduced to less than 160/100 mm Hg before noncardiac surgery. It is to be noted that perioperative hypertension is an important risk factor for postoperative hypertension.

In hypertensive patients with existing but stable end-organ damage, marked fluctuations in blood pressure during anesthesia and surgery may lead to worsening myocardial ischemia, MI, acute renal failure or a cerebrovascular accident. A sharp rise in BP during surgery is best controlled by a titrated IV infusion of nitroglycerin.

Patients who have been receiving a beta-blocker should be continued on the beta-blocker postsurgery, else there is often a rebound hypertension with marked tachycardia. After major surgery severe postoperative pain and hypoxia are two factors that can result in a sharp elevation in the BP, aggravating or inducing end-organ damage, particularly in known hypertensives. Relief of pain and hypoxia generally results in BP control. BP control is important as it reduces the risk of postoperative bleeding, premature graft closure in patients who have undergone coronary artery bypass surgery, and the risk of end-organ damage. A titrated IV infusion of nitroglycerin is the drug of choice in the postcoronary bypass hypertensive patient.

Acute Hypertension in Patients on MAO Inhibitors

Ingestion of food containing tyramine or sympathomimetic amines in patients on MAO inhibitors can lead to an acute hypertensive crisis. Tyramine is metabolized by an alternative pathway to octopamine, which release catecholamines from peripheral sites causing acute hypertension. This episodic hypertension is dangerous, particularly in known hypertensives. Fortunately, these episodes are self limited and last just for 4–8 hours. Tyramine containing foods are bananas, coffee, chocolate, soya sauce, avocadoes, chicken liver, unpasteurized cheese, Chianti wine and certain beers. These foods should be strictly avoided by patients on MAO inhibitors.

Hypertensive crisis seen in pheochromocytoma is dealt with under Endocrine Emergencies, and hypertensive crisis in eclampsia is further dealt with in the Section Critical Care in Pregnancy.

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DISSECTION OF THE AORTA

INTRODUCTION

Aortic dissection is a catastrophic emergency most frequently associated with hypertension. Dissection occurs through a tear in the intima, and this takes place either in the ascending aorta or at the beginning of the descending aorta, distal to the origin of the left subclavian. Blood dissects the aorta between the intima and the media for a varying length, with catastrophic results. The condition is more common in men than in women, and the mortality is over 50% in the first 48 hours, and over 70% within the first week. Rarely aortic dissection can occur in the absence of hypertension in patients with a congenital weakness in the aortic wall as in Marfan's syndrome, or in aortic cystic medionecrosis.

CLASSIFICATION

A classification of aortic dissections based on approach to therapy, delineates three types: Types A, B and C, which have been illustrated in Figure 1.

A more current classification is that proposed by the Stanford group of workers.[1] This classification delineates just two types—(1) Type A and (2) Type B. In Type A, the ascending aorta is involved, irrespective of the site of intimal tear. 15% of tears in the transverse aorta and 5% of tears in the descending aorta also involve the ascending aorta. In Type B, only the descending aorta beyond the left subclavian is involved. The risk of sudden death is highest in Type A as the dissection can cause tamponade, aortic insufficiency, congestive heart failure and coronary occlusion. Type B dissections carry less risk and therefore can be managed conservatively.

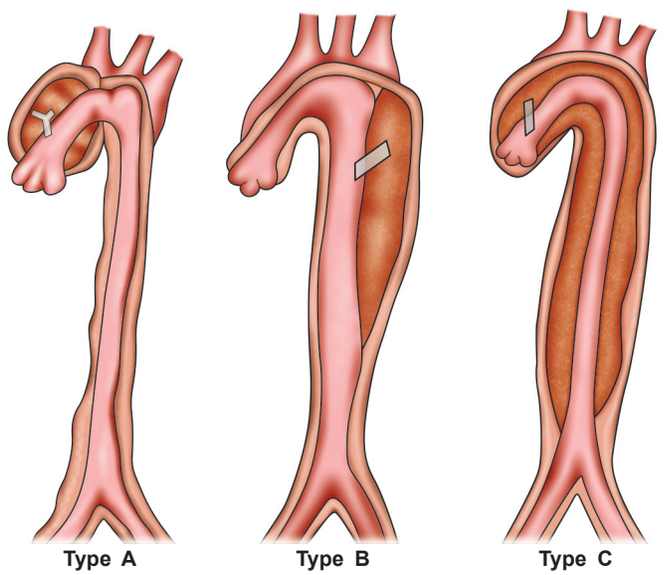


Fig. 1: Classification of aortic dissections. Type A dissection: Dissections proximal to origin of left subclavian artery. Type B dissection: Tear distal to origin of left subclavian artery with no involvement of the ascending aorta. Type C dissection: Dissection extends both proximally and distally to origin of left subclavian artery. The current standard classification recognizes two types: (1) Type A, when the ascending aorta is involved, irrespective of the site of tear; (2) Type B, when only the descending aorta distal to the origin of the left subclavin artery is involved

CLINICAL FEATURES AND DIAGNOSIS[2,3]

Excruciating pain starting most often in the back is the presenting feature. The pain is also felt in the front of the chest and may radiate to the shoulders and the left arm, or to both arms. Invariably the patient is admitted to the intensive care unit with a diagnosis of acute MI. The correct diagnosis depends on a high index of suspicion. The clinical features of shock often accompany the agonizing pain, but a noteworthy feature in a number of these patients is the persistence of hypertension in the presence of other shock-like features.

Clinical features that must be carefully searched for are—

- An inequality of pulses in the upper limbs, or the disappearance of the pulse in an upper limb or even a lower limb.
- The appearance of a rough systolic murmur at the base, or over one or both carotids.
- Pulsations over one or the other sternoclavicular joint.
- The development of a diastolic murmur of aortic incompetence. At times, a soft systolic or even continuous murmur is heard over the middle of the back in extensive dissection of the thoracic aorta.
- Focal neurological signs, if dissection involves the carotid or vertebral arteries, with compression of the lumen of these vessels.
- The absence of classical ECG changes of myocardial infarction, and no rise in creatinine kinase isoenzyme (CK-MB) or troponin levels in blood, in spite of severe pain compatible with MI.
- Extremely wide radiation of pain, which may be felt over the lower thoracic spine, the small of the back, in the abdomen, and even involving the lower extremities. This should suggest a possible extensive dissection.

A hemorrhagic left-sided pleural effusion, when associated with the clinical features of an acute MI should also suggest the diagnosis of an aortic dissection. The pleural effusion is due to a slight leak of the dissection into the pleura, or at times due to pleural irritation.

About one-third of patients with dissection of the aorta present with manifestations of compromised flow to a major branch of the aorta. This is due to compression or thrombosis of the true lumen of a major branch as a result of pressure from the blood within the expanded false lumen. When the carotids and vertebrals are involved, the presentation is with a neurological deficit or a stroke; involvement of the subclavian causes ischemia to the upper limb; involvement of the mesenteric artery results in intestinal ischemia; involvement

of a renal artery results in renal failure or hypertension and of the iliofemoral vessels in lower limb ischemia.

Sudden death can occur from rupture of the dissected aorta into the pleura, the pericardium (causing cardiac tamponade), the retroperitoneum or into the abdomen.

INVESTIGATIONS

An X-ray of the chest shows a widened mediastinum in 50% of cases. A double contour of the arch at the start of the descending aorta, may occasionally suggest the diagnosis. A small left sided pleural effusion may occasionally be observed when the adventitia oozes red blood cells from the dissecting hematoma. A progressive widening of the mediastinal shadow strongly suggests the diagnosis.

Echocardiography Transesophageal echocardiography (with the probe within the esophagus) is a very useful non-invasive method of demonstrating a dissection, and also of demonstrating the intimal flap, which points to the site of the dissection.[4]

A computed tomography (CT) scan or an MRI of the thorax invariably proves a dissection, clearly demonstrating the double lumen in the aorta, and often pointing to the site or origin of the dissection (Figs 2A and B).[5]

Most surgeons before surgery prefer to have an anatomical display of the dissection through an aortography. This indeed is not required if all the necessary information is available through echocardiography and a CT or MRI of the chest. What is more, if the intimal flap has been sealed off (which may happen within a few days of the dissection), an aortogram may not be able to pick up the dissection. In such patients, if the diagnosis is highly suspect, it is mandatory to do a CT or MRI of the chest, if these investigations have not been done.

MANAGEMENT[6,7]

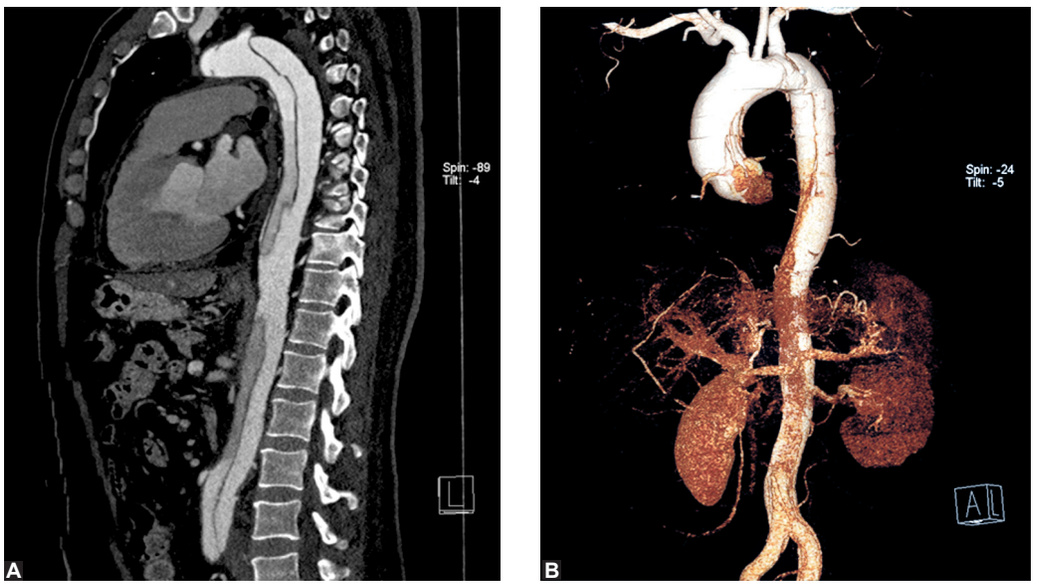
The patient under intensive care should be continuously monitored with regard to vital signs, ECG, relevant investigations on the blood, and serial X-rays of the chest. The BP should be constantly monitored. The principles of management are (Box 2)—

- *Complete bed rest.*
- *Relief of pain* with morphine, buprenorphine or pethidine. Small bolus doses (2–5 mg of morphine) should be given intravenously, and repeated as and when necessary.

Box 2: Principles of management of aortic dissection

- Complete bed rest
  Relief of pain with morphine (2–4 mg IV), or buprenorphine (0.2–0.4 mg IV), or pethidine (75–100 mg IM)
- Quick reduction of blood pressure—In hypertensive patients systolic BP should be maintained between 100–120 mm Hg; in non-hypertensive patients, keep systolic BP around 90 mm Hg. A combination of IV nitroprusside and IV propranolol (0.5–1 mg every 15–30 minutes till beta-blockade achieved), is commonly used. Many units now prefer to use IV labetalol (see text) instead of the above combination
- Medical therapy continued with in the following cases—
  - In patients with uncomplicated Type B dissection (dissection distal to origin of left subclavian artery, with no involvement of the ascending aorta), who have responded well to medical therapy (relief of pain, control of BP), and are hemodynamically stable
  - In patients with stable, chronic dissection (2 weeks or more after onset)
  - Failure of opacification of double lumen on aortography
- Definitive surgical therapy for aortic dissection in selective cases

Abbreviations: IV, intravenous; IM, intramuscular; BP, blood pressure.



Figs 2A and B: Aortic dissections

- *Reduction of blood pressure* This is imperative in all hypertensive patients. The pressure should be quickly and sharply reduced to a systolic of about 100 mm Hg provided tissue perfusion is adequate. It should never exceed 120 mm Hg. In the rare instances when the patient is not hypertensive, the systolic BP should be kept around 90 mm Hg. It is preferable to use intravenous infusions of nitroprusside to lower the blood pressure and to maintain it at the desired level. The method of infusion has already been described earlier. It is important to combine the use of nitroprusside with a beta-blocker. This is because sodium nitroprusside increases the dP/dT, which is a measure of the velocity of left ventricular ejection. An increase in the velocity of left ventricular ejection is an undesired effect in aortic dissection, and can be countered by a beta-blocker, which reduces dP/dT—an advantage in dissection. For an acute or rapid reduction in dP/dT, propranolol is given intravenously in a dose of 0.5–1 mg every 15–30 minutes till satisfactory beta-blockade occurs. For the maintenance of beta-blockade in a stable dissection, propranolol is given orally in a dose 20–40 mg thrice daily.

Many units in the West prefer the use of labetalol to nitroprusside in control of hypertension in aortic dissection. The drug is a selective alpha-blocker and a non-selective beta-blocker, and thereby reduces dP/dT and the systolic BP by beta-blockade and vasodilation. A bolus injection of 0.25 mg/kg is given intravenously over 2 minutes and repeated every 10–15 minutes. The drug can also be given through a continuous infusion at 1–2 mg/minute.

Esmolol, a very short acting β_1 selective receptor blocker is also very useful in the prompt control of acute hypertension in aortic dissection. It is given as an IV bolus in a dose of 500 µg/kg per minute over 11 minutes and then as an infusion of 150–300 µg/kg per minute. The infusion is titrated to keep the systolic BP at 100 mm Hg.

If labetalol and esmolol are unavailable, sodium nitroprusside combined with propranolol or metoprolol are equally effective.

Oral antihypertensives like alpha methyldopa, ACE inhibitors or calcium channel blockers may be used in addition, once the BP has been urgently brought down to a desired level (about 100 mm Hg systolic) with IV parenteral therapy.

Patients who do not tolerate beta-blockade [patients with asthma, congestive heart failure and chronic obstructive pulmonary disease (COPD)] can be treated with trimethaphan, a ganglion blocking agent for a quick reduction in BP. The drug is given in a dose of 1–2 mg/minute in a slow IV infusion for 24–48 hours. The head end of the bed is elevated to maximize the orthostatic hypotension the drug induces and the BP is monitored and maintained around 100 mm Hg systolic. The use of trimethaphan is associated with rapid tachyphylaxis and with unpleasant sideeffects due to ganglion blockade. We have no experience with the drug.

Box 3: Indications for definitive surgical therapy in aortic dissection (surgical expertise and experience mandatory)

- Type A Dissection (dissection starting in proximal aorta)
- Type C Dissection (dissection extends both proximal and distal to origin of left subclavian artery)
- In presence of aortic insufficiency
- Impending rupture of aneurysm (even in Type B variety)
- Compromised blood flow to a major branch of the aorta
- Large hemorrhagic pleural effusion
- Cardiac tamponade
- Failure to control hypertension or pain with medical therapy

Lowering the BP produces dramatic relief in back and chest pain. Once the pain is relieved and the BP lowered, the patient may be sent for a CT or an MRI of the chest, or if needs be for an emergency aortography. An echocardiography can easily be done at the bedside. Esophageal echocardiography as mentioned earlier, is of great help. It must be done expertly without causing a rise in the BP during passage of the probe into the esophagus.

Medical therapy is continued for a Type B tear, i.e. a tear distal to the origin of the left subclavian in which the ascending aorta is uninvolved, provided there is relief of pain, control of BP and a stable clinical state. Other indications for medical therapy are a stable, chronic aneurysm (onset more than 2 weeks), failure of opacification of a double lumen on aortography, and the unavailability of surgical expertise.

The first requisite for surgical therapy is surgical expertise and experience with the problem.[7] If this is available, the indications for surgery include a Type A dissection (dissection starting in and only involving the proximal aorta), Type C dissection (where dissection extends both proximal to the origin of the left subclavian, and also extends distal to it). Other indications for surgery are aortic insufficiency, impending rupture of the aneurysm (even in the Type B variety), a large hemorrhagic pleural effusion, cardiac tamponade, and inability to control pain or reduce hypertension with drug therapy. Indications for definitive surgical therapy are listed in Box 3. Surgical therapy involves resection and graft replacement. Successful medical or surgical therapy should be followed-up by the continued use of antihypertensive drugs which should include a beta-blocker.

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CHAPTER 27

Pulmonary Embolism

INTRODUCTION AND IMPORTANCE[1]

Pulmonary embolism (PE) is the third most common cause of mortality after coronary artery disease and stroke. It is the commonest cause of death in the puerperium and postoperative period. Despite its importance, it remains underdiagnosed in our country and hence in a sense neglected. Indeed, up to 80% of pulmonary emboli found at autopsy had not been suspected antemortem. This must be one of the most staggeringly poor diagnostic rates for any disease in all of medicine. Despite all the advances in diagnosis, this appalling diagnostic rate has not changed over the last four decades. Sadly, physicians cannot diagnose what they do not suspect and this is the crux of the problem with PE as we shall discuss later in the chapter.

The problems in PE in the intensive care unit (ICU) are twofold—

1. It can occur as a complication in patients who are already critically ill with diverse medical and surgical problems. The manifestations may be subtle, and the diagnosis in these patients is difficult to make, and at times difficult to confirm. The usual modes of treatment in many of these critically ill patients are hazardous. The importance of being reasonably certain of the diagnosis, before starting potentially hazardous therapy is therefore evident.
2. Patients with PE may also present with acute cardiorespiratory failure. When this occurs against a background of recovery from recent surgery, the diagnosis is generally obvious, and the management well-defined. When acute cardiorespiratory failure due to PE occurs against a background unrelated to surgery, the diagnosis may be often missed with disastrous consequences.

Pulmonary embolism is believed to affect 600,000 patients annually in the US. Of these, 200,000 die from their PE. It is responsible for at least 15% of all hospital deaths in some hospital mortality series from the US. It is unfortunately, still the general belief that PE within or outside the ICU is comparatively uncommon in India when compared to the West. This is untrue; the incidence of PE is about the same. In our critical care unit, the incidence of PE is very close to that observed in the West. In 2006, Kapadia SR and colleagues from Sir Ganga Ram Hospital, New Delhi[2] noted that PE occurred in as many as 40% of 1,552 consecutive Indian patients with symptomatic deep vein thrombosis (DVT); 47% of patients with PE judged from a high-probability lung perfusion scan were asymptomatic. Considering that many patients with DVT are asymptomatic, the incidence of both DVT and PE would be much higher than is apparent. Increasing awareness will perhaps provide a much clearer idea about the prevalence of venous thromboembolism in India, which is certainly much higher than what is generally believed.

SOURCES OF PULMONARY EMBOLISM

The two main sources of embolism are venous thrombosis in the lower limbs, thrombi within the right atrium in patients with atrial fibrillation, and other supraventricular arrhythmias. Thrombi within the right ventricle causing PE can occur following septal infarction or a right ventricular (RV) infarction.

Conditions that lead to venous stasis, endothelial cell damage and a subclinical hypercoagulable state, predispose to venous thrombosis. Venous thrombi in the legs leading to thromboembolism are most frequent in the popliteal veins above the knee, and in the femoral vein within the thigh. Rarely, thrombi within the pelvic veins may also lead to PE.

Deep vein thrombosis in the calves is common; generally, these thrombi extend upward into the popliteal veins before thromboembolism occurs.

Risk factors of venous thrombosis in the lower limbs include trauma to a limb, generalized trauma, immobilization of a limb, complete bed rest, sitting for long periods, as in air, train or vehicular travel, congestive heart failure, recent surgery, pregnancy, pelvic disease and recent myocardial infarction. Femoral and popliteal vein thromboses with thromboembolism are important complications of total hip or knee replacement surgery. Both oral contraceptives and postmenopausal hormone replacement therapy increase the risk of venous thromboembolism. The pulmonologist must not forget that chronic obstructive pulmonary disease (COPD) is an important risk factor both for DVT and PE. Cancer promotes the production of procoagulant factors and is an important risk factor in venous thrombosis and thromboembolism. Occassionally, venous thrombi in the legs and thromboembolism is a manifestation of an occult cancer, in particular, cancer of the pancreas, ovary and a primary cancer of the liver. Any acute critical illness requiring intensive care may perhaps be associated with an increased incidence of venous thrombosis. Current data have identified heavy smoking and hypertension as new independent risk factors for DVT.

In patients who present with venous thrombosis with or without thromboembolism, and who have no risk factors, it is important to test for hypercoagulable states, either genetic or acquired. There have been major advances in our knowledge of the molecular markers of thrombophilic states. The two most important are the Leiden mutation of Factor V, which confers a resistance to activated protein C, and the G20210A mutation of prothrombin. Both these occur in about 4% of the Caucasian population. Other rarer genetic defects include antithrombin deficiency (0.02%), protein C deficiency (0.2%), and protein S deficiency (0.1%). Similar data from Indian populations are needed but at present lacking. Intriguingly, Factor V Leiden and prothrombin mutation are stronger risk factors for DVT than PE. Occasional patients are heterozygous for two of these anomalies and then carry a much greater thrombotic risk. Conversely, certain genetic traits offer protection. This includes the O blood group which appears to reduce the risk of DVT even in carriers of Factor V Leiden. Elevated level of homocysteine is also an independent risk factor though the genetics of transmission are not as yet clear. A detailed genetic prothrombotic screen should be mandatory in patients with a history of DVT or PE occurring without any other traditional risk factor; in those with a positive family history; those with recurrent episodes of thrombosis; patients with their initial thrombotic episode at a young age; and in patients with arterial and venous thrombosis or thrombosis in unusual sites.

Acquired factors causing thrombophilia include the presence of lupus anticoagulant and antiphospholipid antibodies, which predispose chiefly to venous but also to arterial thrombosis (Box 1).

Box 1: Important risk factors for deep vein thrombosis and pulmonary embolism

- *Surgery—*
  - Major abdominal, pelvic surgery
  - Hip, knee surgery
  - Trauma
  - Fractures
  - Spinal cord injury
- *Immobilization—*
  - Hemiplegia
  - Paraplegia
  - Prolonged recumbency
- *Obstetrics—*
  - Pregnancy
  - Puerperium
- *Airplane, train, car travel*
- *Hormonal treatment—*
  - Oral contraceptives
  - Hormone replacement therapy
  - Tamoxifen, raloxifene
- *Cardiorespiratory—*
  - Congestive cardiac failure
  - Atrial fibrillation, supraventricular tachycardia
  - Myocardial infarction: septal infarct, right ventricular infarction
  - Cardiomyopathy
  - Bacterial vegetations on the tricuspid valve
  - Chronic obstructive pulmonary disease
- *Past history of DVT/PE*
- *Malignancy—*
  - Abdominal, pelvic
  - Advanced, metastatic
  - Concurrent chemotherapy
- *Inflammatory bowel disease*
- *Nephrotic syndrome*
- *Obesity*
- *Genetic factors —*
  - Factor V Leiden disease
  - Protein C and Protein S deficiency
- *Acquired thrombophilia*
- *Lupus anticoagulant*
- *Antiphospholipid antibody syndrome*

Venous thrombosis in the upper limbs is uncommonly associated with PE. However, if the patient has had a central venous line for many weeks or has a Hickman's catheter, there is a definite risk of thrombus formation in the central vein, even if the central line has been changed periodically. Occasionally, massive fatal PE resulting from such a thrombus may be seen.

Very rarely in the ICU, a catheter tip of a central venous line is sawed off by the bevel or the point of the large needle through which the catheter is introduced. This tip may travel to the lung and produce PE.

Fat embolism after fractures and crush injuries should always be kept in mind. Air embolism following accidental injection of a large bolus of air (or following entry of air from other causes) into the systemic venous circulation, or tumor

emboli particularly in hypernephromas, or from other tumor tissue gaining access to the venous circulation, may also be occasionally observed.

PATHOPHYSIOLOGY

The clinical features of PE are due to three possible pathophysiological changes—

- *Acute circulatory compromise* due to an obstructed pulmonary circulation. This occurs with massive embolism or when numerous thromboemboli block a large cross-section of the pulmonary circulation (>60–70% of the circulation). This circulatory compromise is characterized by pulmonary hypertension (PH), RV dilatation and dysfunction, right-sided heart failure and a low cardiac output, which when marked leads to cardiogenic shock. The dilated right ventricle causes a septal shift to the left, resulting in underfilling of the left ventricle, a decreased systemic cardiac output and myocardial ischemia from reduced coronary perfusion.
- *Gas exchange abnormalities* generally characterized by a low PaO_2 with a lowered $PaCO_2$ High V/Q areas are responsible for increased dead space ventilation. Tachypnea and an increased minute ventilation allow a normal, and often a lower than normal $PaCO_2$ to be maintained. If the dead space is markedly increased, and the minute ventilation does not increase proportionately, the $PaCO_2$ may rise. The alveolar PCO_2 is characteristically slightly lower than the arterial $PaCO_2$.

  Normal arterial blood gases do not exclude PE. In fact, arterial hypoxemia is generally never marked, except in massive embolism associated with a shock-like state. The PaO_2 is rarely less than 55 mm Hg. A lowered PaO_2 is due to ventilation-perfusion mismatch resulting from atelectasis, and to redistribution of pulmonary blood flow, which causes a fall in the V/Q ratio in areas of the lung that are unobstructed by pulmonary emboli.
- *Pulmonary infarction may* occur but is not commonly observed in PE. Patients with congestive heart failure are more prone to develop pulmonary infarction because of pre-existing raised pulmonary venous pressure.

  The clinical manifestations of thromboembolism often appear to be far more serious than what is expected from the degree of vascular occlusion. In critically ill patients in the ICU, this could be due to two causes: (1) a poor pre-existing cardiopulmonary reserve; (2) release of vasoactive and bronchoconstrictive mediators from platelets and perhaps from other sources, following embolism. This potentiates PH, accentuates ventilation-perfusion disturbances, and adds to the already existing tachypnea.

PULMONARY EMBOLISM SPECTRUM

The outcome following PE is a function of the size of the PE and the underlying cardiopulmonary status. A small PE may be poorly tolerated and tip the balance in a patient with advanced COPD while an otherwise fit young person might tolerate the effects of a larger PE without compromise. There is a spectrum in the severity of the PE, from mild to massive. At one end, the patient with mild PE may remain asymptomatic with the PE detected incidentally. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study,[3] there were 20 such patients who had mild PE, which was not initially diagnosed and hence not treated.

The mortality in these patients, even when untreated, was only 5%. At the other end of severity is a massive PE, which can cause almost immediate cardiorespiratory arrest. A massive PE is one that results in hemodynamic instability. Overall, these PEs are rare; in the PIOPED II series,[4] only 10% of all PEs could be classified as massive. The majority of PEs fall in between these two groups. This category includes submassive PE. These are patients with a sizeable clot burden, no hemodynamic instability when they first present, but show echocardiographic evidence of right heart dysfunction. These patients will be discussed in more detail later.

CLINICAL FEATURES: PULMONARY EMBOLISM SYNDROMES

The symptoms of PE are nonspecific and include dyspnea, chest pain, fever, cough, hemoptysis and apprehension. The signs are equally nonspecific and include tachypnea, tachycardia, auscultatory crackles, a pleural rub and an accentuated pulmonary component of the second heart sound. Evidence of an associated DVT must be carefully looked for, though this is often not clinically obvious. Because the symptoms and signs are nonspecific, attempts have been made to combine them into scoring systems. The best validated is that of Wells,[5] which can immediately be applied at the bedside on first seeing a patient. It gives the patient points based on previous PE/DVT; heart rate greater than 100/minute; recent surgery or immobilization; clinical signs of DVT; alternative diagnosis less likely than PE; hemoptysis and cancer. This scoring system can be applied to inpatients and outpatients and has recently been externally validated. Adding on D-dimer further increases the accuracy of this clinical prediction system (Table 1).

The presentation of PE in the ICU is varied. The clinical syndromes are as follows—

1. Sudden death.
2. Shock, with a low output hypotensive state. Severe chest pain (indistinguishable from the pain of acute myocardial infarction) may or may not be associated with the shock-like state.
3. Acute right heart failure, with increase in the central venous pressure (CVP), prominent "a" waves in the jugular veins, and auscultatory evidence of PH.
4. Acute respiratory failur, with dyspnea, tachypnea, and at times, cyanosis.
5. Features of (2), (3) and (4) are combined in massive embolism: various combinations are observed depending on the interval after acute embolism. Shock often predominates in the earliest phase and is associated with a

Table 1: Wells clinical prediction rule for pulmonary embolism

Clinical feature	*Points*
Clinical symptoms of DVT	3.0
Other diagnosis less likely than PE	3.0
Heart rate greater than 100 beats per minute	1.5
Immobilization or surgery within past 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Total	

Abbreviations: PE, pulmonary embolism; DVT, deep venous thrombosis.
Risk score interpretation (probability of PE):
>6 points: high risk (78.4%)
2–6 points: moderate risk (27.8%)
<2 points: low risk (3.4%)

Box 2: Syndromes associated with pulmonary embolism

- Pulmonary infarction syndrome
- Isolated dyspnea syndrome
- Syndromes associated with massive pulmonary embolism manifesting as—
  1. Sudden death
  2. Shock and/or prolonged syncope
  3. Acute right heart failure
  4. Acute respiratory failure
  5. Severe bronchospasm and pulmonary edema
  6. Combination of (2), (3), (4) and (5)
- Subtle features like unexplained tachycardia, increasingly unstable circulatory state, supraventricular arrhythmia, unexplained tachypnea, postural hypotension or syncope

Box 3: Diagnostic tests for pulmonary embolism

- Chest radiograph
- Electrocardiogram
- D-dimer
- Lower limb venous compression ultrasonography
- Arterial blood gases
- Echocardiography
- Ventilation/perfusion lung scintigraphy
- Helical CT pulmonary angiography
- Pulmonary angiography

raised CVP, hypotension and hypoxic respiratory failure. If recovery ensues, features of PH become more evident.

6. Rarely, massive PE causes acute pulmonary edema or overwhelming bronchoconstriction.
7. Less massive, frequent, multiple, small emboli in already critically ill patients may show very subtle features. These include tachycardia, an increasingly unstable circulatory state, and supraventricular tachycardia. Tachypnea (at times episodic), faintness or actual syncope, particularly on changing from the supine to the sitting posture, may also be observed. There may be an unexplained fall in the PaO_2 or an increase in an already existing hypoxia. Sometimes, a rapid deterioration in the clinical state of a seriously ill individual, a low-grade fever, a high ESR without apparent cause; or unexplained icterus may be related to silent PE. All these subtle features described above unfortunately lack specificity and sensitivity and may well be due as much to the critical illness per se, as to a complicating PE.
8. Pulmonary infarction. Pulmonary infarction is not frequently observed. When it does occur, its significance should not be missed. Hemoptysis, pleural pain and an unexplained occurrence of a pleural effusion in a critically ill patient suggest embolism. One or more shadows within the lung, or other radiological features compatible with PE should also prompt a correct clinical diagnosis.

Clinical evidence of accompanying venous thrombosis in the lower limbs and the presence of atrial fibrillation are the strongest pointers to a possible PE. Among the significant features to be looked out for in the clinical diagnosis of DVT, are tenderness and swelling of the calf muscles; pain in the calf on dorsiflexion of the foot (Homan's sign), rise in the skin temperature of one limb, edema of the leg or foot, and delayed cooling of an exposed lower limb (Provan's sign). One or more of these signs are positive in 50% of patients with PE. *However, absence of clinical signs in no way excludes femoral, popliteal or deep vein thrombosis (Box 2).*

DIAGNOSTIC TESTS (BOX 3)[6,7]

Chest Radiograph (Figs 1 and 2)

The chest radiograph can be normal though this is rare with massive PE. In the PIOPED series[4] of massive PE, only 16% of patients had a normal chest radiograph. Focal oligemia, if carefully looked for, will be noted in 40–80% of patients. Plate-like atelectasis, basal wedge-shaped shadows and pleural effusions are other distinctive but nonspecific radiological manifestations. The presence of pre-existing cardiopulmonary disease makes appreciation of these features even more difficult. The chest radiograph is also invaluable in patients with PE for differential diagnosis of other conditions like pneumonia, left ventricular failure or pneumothorax.

Electrocardiogram[8]

The electrocardiogram (ECG) is usually normal in smaller PE. In massive PE, a normal ECG is uncommon but did occur in as many as 30% of PIOPED patients with major PE. Transient ST-T changes are the commonest ECG manifestations and may

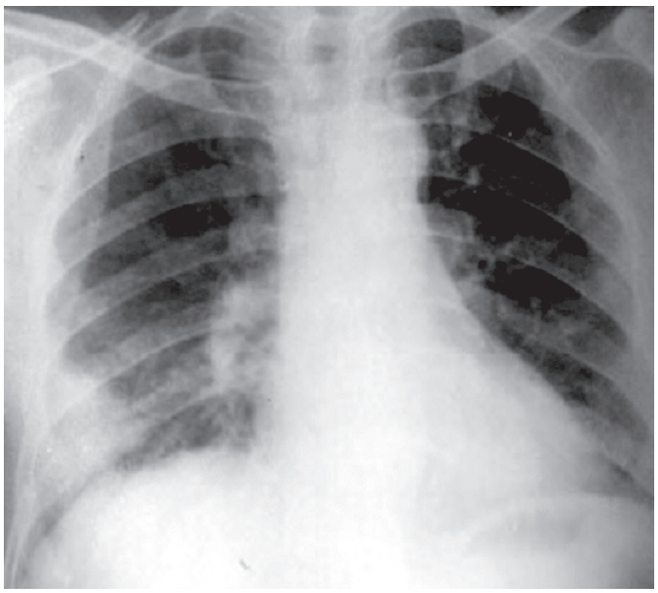


Fig. 1: Chest X-ray demonstrates a wedge-shaped opacity in the right lower zone with its apex pointing to the hilum representing a pulmonary infarct. Note the enlarged and prominent right pulmonary artery (Westermark sign)

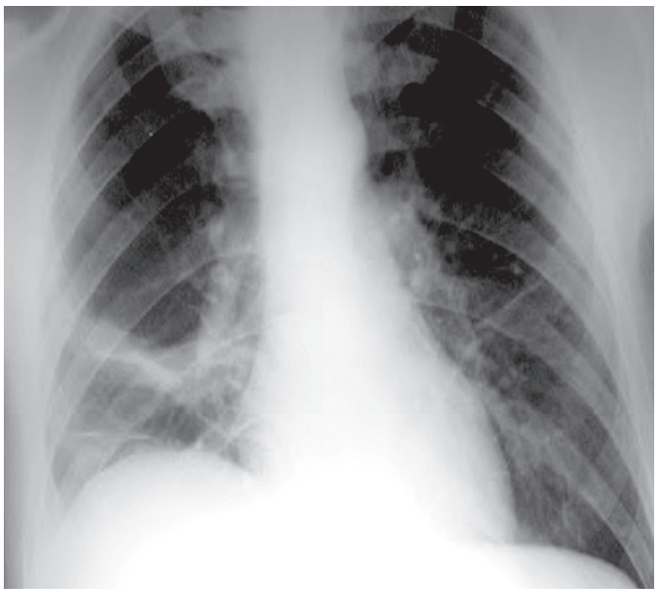


Fig. 2: Pulmonary infarct. Chest X-ray demonstrates a linear band in the right lower zone with an elevated right dome of diaphragm. The linear band represents an infarct with elevation of the right dome due to underlying volume loss. An atelectatic band is also seen in the left lower zone representing an infarct

occur in 50–70% of patients. A $S_1Q_3T_3$ pattern may be seen, along with transient right bundle branch block (RBBB) or atrial fibrillation. Anterior lead T-wave inversion is the pattern that best correlates with the severity of the PE, occurring in 90% of massive compared to 20% of nonmassive PE.

D-Dimer

D-dimer is a breakdown product of cross-linked fibrin and is sensitive marker of acute thrombosis. A normal D-dimer in a low clinical probability setting is an accurate way of ruling out PE. On the other hand, though the D-dimer is very specific for fibrin, the specificity of this test for PE is poor, because fibrin is produced in a variety of conditions including inflammation, infection, necrosis and cancer. Hence, a D-dimer above 500 μg/L has a poor positive predictive value for PE and cannot reliably rule in the disease. But a D-dimer level below this cut-off value reliably rules it out, especially in a low probability setting. Nuclear scanning or spiral computed tomography (CT) angiography may not be needed in this group. There are presently four different assays available and it is important to use the highly sensitive enzyme-linked immunosorbent assay (ELISA) or automated turbidimetric assay to get the most sensitive results. Results are generally available at the bedside in an hour, making this a cost-effective and useful screening test.

Lower Limb Venous Compression Ultrasonography[9]

In studies using venography as the gold standard for detecting proximal DVT, lower limb venous compression ultrasonography, an entirely noninvasive test, had a sensitivity of 97% and a specificity of 98% for symptomatic, proximal DVT. The absence of full compressibility of the deep vein on applying pressure through the ultrasound probe is the single best validated diagnostic criterion. The advantage of this test is that it is noninvasive and can be performed at the bedside. The finding of DVT by ultrasonography in a patient with suspected PE is sufficient evidence to commence anticoagulant therapy without any further testing. Approximately, 50% of PE suspects will have evidence of DVT on sonography, and further invasive and costly tests are not required in these patients. The exact position of ultrasonography in the diagnostic algorithm of PE is still being refined.

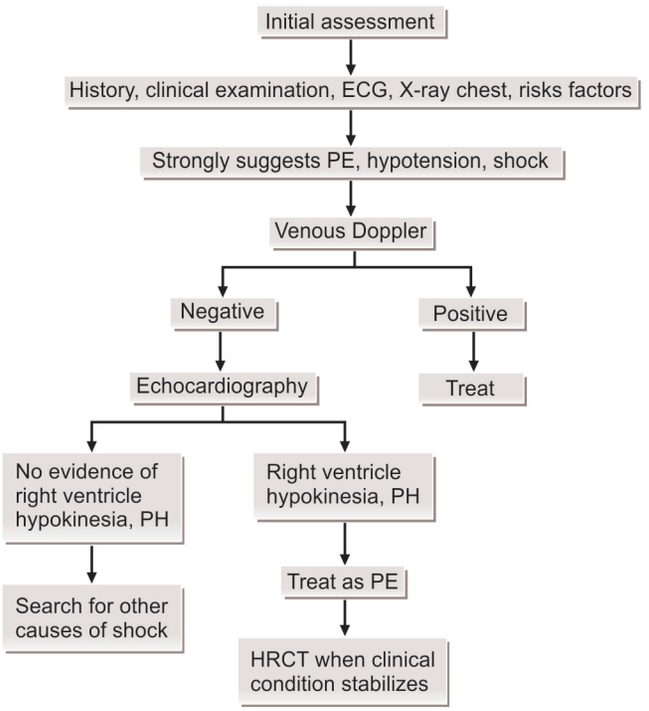
Arterial Blood Gases

Hypoxia is usual but not universal following a major PE. Approximately, 20% of patients with proven PE will have a normal arterial oxygen pressure and alveolar arterial oxygen gradient.

Echocardiography[10] (Flowchart 1)

Echocardiography is an enormously useful test to detect the presence and severity of RV pressure overload. RV dysfunction (RV dilatation, hypokinesia) on ECHO helps in stratification of these patients. If present, it denotes greater than 50% obstruction to the pulmonary circuit. Other echocardiographic findings include: increased RV/LV diameter ratio, paradoxical septal motion, pulmonary artery dilatation and evidence of tricuspid regurgitation. The sensitivity of these signs which are often combined is between

Flowchart 1: Algorithm for role of echocardiography in the diagnosis of massive or sub-massive pulmonary embolism



Abbreviations: HRCT, high resolution computed tomography; ECG, electrocardiogram; PE, pulmonary embolism; PH, pulmonary hypertension.

Box 4: Modified PIOPED criteria for lung scan interpretation

- High probability—
  - 2 or more large mismatched perfusion lung scan defects
    or
  - 2 or more moderate + 1 large mismatched perfusion lung scan defect
    or
  - 4 or more moderate mismatched perfusion lung scan defects
- Intermediate probability—
  - Borderline high or borderline low
  - Not falling into high, low or normal categories
- Low probability—
  - Nonsegmental perfusion defects only
    or
  - 1 moderate mismatched segmental perfusion defect with normal chest X-ray
    or
  - Any perfusion defect with a larger abnormality on chest X-ray
- Normal—
  - No perfusion defects
  - Perfusion outlines exactly the same as shape of lungs on chest X-ray

40% and 70% in patients with clinically suspected PE and their specificity approaches 90%. Thus, echocardiography has emerged as a first-line test in patients with suspected massive PE. *It is extremely useful in the differential diagnosis of shock due to massive PE from cardiogenic shock, cardiac tamponade, valvular heart disease and aortic dissection*. Indeed, absence of PH and/or RV dilatation and hypokinesia makes PE as the cause of shock unlikely. In a small subset of patients with PE, transthoracic echocardiography allows a direct visualization of the clot in the right heart chambers or in the right main pulmonary artery.

Ventilation/Perfusion Lung Scintigraphy

The landmark PIOPED study[3] showed us that V/Q scanning retains its importance. The perfusion scan is done by injection of albumin macroaggregates labeled by technetium-99m. The macroaggregates are trapped in approximately 0.1% of the pulmonary capillary circuit and may be imaged by a gamma camera. Any disease that narrows the airways or fills the alveoli will result in hypoxic pulmonary vasoconstriction; hence, this pattern is not highly specific for PE. If the perfusion defect is large or segmental, it makes the diagnosis more likely. The addition of ventilation scintigraphy by xenon-133 or aerosolized technetium-99m further increases the specificity. This so-called mismatched defect, i.e. perfusion defect with normal ventilation, is highly predictive of PE. Based on revised data from the PIOPED study, lung scans are currently classified into normal, high probability and nondiagnostic. The high negative predictive value of a normal lung scan has been confirmed by several studies including a large outcome study. Equally useful is the positive predictive value of a high probability scan (around 90%) and this is sufficient evidence to rule in PE and proceed with treatment without subjecting the patient to further testing. Recent evidence suggests that a chest radiograph may replace the ventilation scan and be combined with a perfusion scan to give excellent overall agreement of 88% and positive predictive value of 86% for a scintigraphic mismatch. Unfortunately, in the latest study from Wells and his group,[11] only 41% of all V/Q scans fell into the normal or high probability group. The majority were nondiagnostic. These scans carry a 30% likelihood of PE and hence the majority (around 60%) of patients who undergo V/Q scanning will need to undergo further tests to rule in or rule out suspected PE. *For this reason and because it is inconvenient and often impossible to transport a critically ill patient to the nuclear medicine department, the ventilation scintigraphy scan is rarely used for diagnosis of PE in the ICU. Nevertheless, one must be aware of this diagnostic modality (Box 4).*

Helical CT Pulmonary Angiography[12] (Figs 3 and 4)

This noninvasive test offers excellent imaging of the pulmonary vasculature. It has by and large replaced V/Q scanning as a diagnostic modality for PE and has nearly (if not

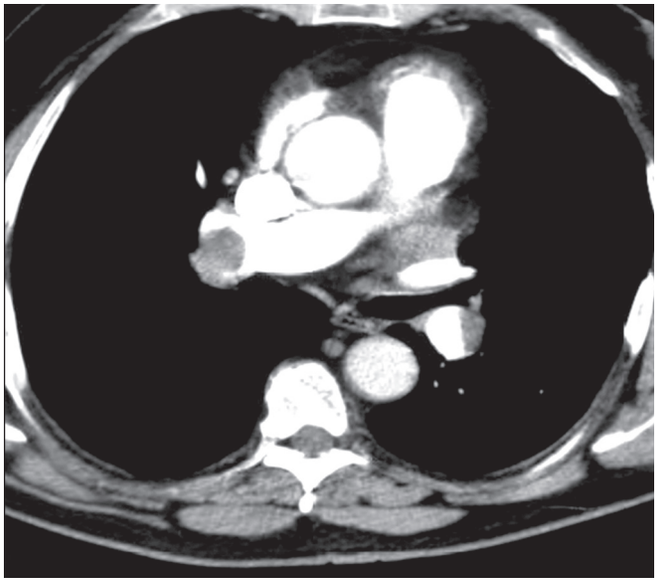
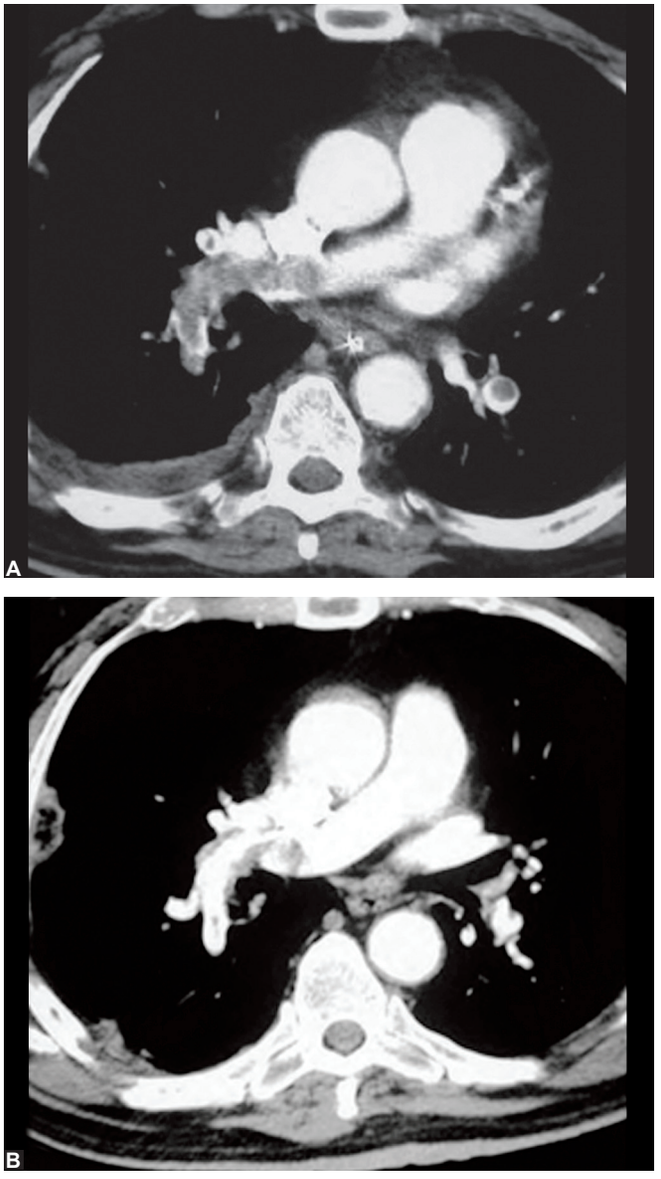


Fig. 3: Bilateral pulmonary emboli. Computed tomography angiography demonstrates pulmonary emboli in both pulmonary arteries



Figs 4A and B: Pulmonary emboli. Computed tomography angiography demonstrates a large embolus in the right pulmonary artery and a smaller embolus in the left pulmonary artery

completely) eliminated the need for invasive pulmonary angiography. Newer and still evolving technology used in helical CT pulmonary angiography has further increased the sensitivity and specificity for detecting PE, the sensitivity ranging from 83% to 100% and specificity from 89% to 97%. This sensitivity and specificity favors comparably with that observed in invasive pulmonary angiography. The advantages of CT angiography when compared to V/Q screening and invasive pulmonary angiography are summarized below—

- Computed tomography angiography is noninvasive, convenient and can be performed safely and quickly in critically ill patients, particularly those in shock and/or in acute right heart failure.
- Studies comparing CT angiography to V/Q scanning suggest that CT angiography is a better test because of more frequent definitive confirmation of pulmonary emboli.
- In a critically ill individual, there is often a large differential diagnosis to PE. A CT angiography offers evidence of other causes as well as that of PE, which neither a V/Q scan nor invasive pulmonary angiography can provide.
- Computed tomography angiography of the legs and pelvis could be performed with the same contrast injection used to image the pulmonary vasculature. Detection of DVT in the femoropopliteal veins is as accurate as with ultrasonography. This procedure could also detect clots in the iliac, renal and caval veins, which are ultrasonographically inaccessible. The major limitation of helical CT pulmonary angiography is the inability to diagnose subsegmental branch emboli, with sufficient certainty. However, invasive pulmonary angiography also has significant limitations in detecting isolated subsegmental emboli. The only other major limitation of helical CT pulmonary angiography compared to V/Q scanning is the need to use contrast material, precluding its use in patients with renal failure and in patients allergic to the dye. It is also inadvisable to use this modality in pregnant women.

What does then one do in a patient with renal failure or in a pregnant woman clinically suspected of serious PE? If DVT or atrial fibrillation is present, one should proceed on the assumption that one is dealing with PE. In the presence of hemodynamic instability, a 2D-ECHO is of immense help. The presence of RV dilatation and PH points to PE.

Pulmonary Angiography

The role of pulmonary angiography in the diagnosis of PE is now sharply reduced. Perhaps, a helical pulmonary CT

angiography might miss out on subsegmental pulmonary emboli which an invasive CT angiography would detect. But is it necessary to diagnose with certainty subsegmental emboli? Data from three large studies suggests that underdiagnosing subsegmental emboli by avoiding pulmonary angiography does not affect the clinical outcomes of recurrent embolism or death.[13] A clinical outcome approach is as safe as the PIOPED approach, less expensive, more convenient, less fraught with immediate risks to the patient and more acceptable to the patient and the physician.

PRINCIPLES OF MANAGEMENT

- *Use of anticoagulants or the use of thrombolytic therapy for the purpose of dissolution of thrombi obstructing the pulmonary circulation. This therapy also helps in dissolution of thrombi in the leg veins, and prevents further embolization.*
- *Cardiorespiratory support in patients with major or massive embolism.*
- *Preventive measures.*

USE OF ANTICOAGULANTS[14]

Unfractionated Heparin

Heparin forms the mainstay of treatment. Unfractionated heparin is started after the diagnosis is made. Around 5,000–7,500 units are given intravenously as a bolus dose, followed by a continuous microdrip infusion at the rate of 1,000 units/hour. The dose is adjusted so as to keep the activated partial thromboplastin time (APTT) to about twice the normal value. Initially, this is measured every 6 hours, and then once or twice daily.

It is important to ensure that the requisite rise in the APTT is quickly achieved, and constantly maintained. If the APTT done after the first 6 hours has not risen to the desired therapeutic range, the 24 hour dose of heparin is increased by 2,000–4,000 units, and the APTT is repeated after 6 hours. Conversely, if the APTT is greater than the therapeutic range of 2.5 times the normal value, the 24-hour dose of heparin is reduced by 2,000–4,000 units, followed by a repeat APTT after 6 hours.

Proper heparinization leads to a decrease in the rate of further embolization to less than 5%. Till recently, it was recommended that warfarin (a vitamin K antagonist) should be introduced only after 5–6 days of IV heparin by which time the APTT is raised to twice the control. Once introduced, warfarin is given daily in a titrated dose to raise the international normalized ratio (INR) between 2 and 3. Parenteral heparin is omitted when this target INR is achieved, and warfarin continued so that the INR is maintained between 2 and 3. It was believed that if warfarin is introduced early in an active thrombotic state, there is a fall in Protein C and Protein S, with an increase in the thrombogenic potential. An overlap with heparin was believed to prevent this.

However, the current American College of Chest Physicians (ACCP) recommendation[13] for the treatment of both deep vein thrombosis and PE is that a vitamin K antagonist (warfarin) should be started early, on the same day as parenteral heparin. Parenteral anticoagulation with heparin should be continued for a minimum of 5 days and until the INR is 2.0 or above for at least 24 hours.

Heparinization can be achieved by IV unfractionated heparin (UFH) as mentioned above, by subcutaneous UFH, by low molecular weight heparin (LMWH) or by fondaparinux. The ACCP 2012 guidelines suggested the use of LMWH or fondaparinux (a factor Xa inhibitor) over IV UFH and over subcutaneous UFH both for the prevention and treatment of DVT and PE.

If there are contraindications to anticoagulation, the guidelines recommend the use of an inferior vena cava (IVC) filter if there is DVT, and pneumatic compression of the legs as prophylaxis for DVT. The ACCP recommends against the use of an IVC filter in addition to anticoagulation. The use of the IVC filter is discussed at length later in this chapter.

Low Molecular Weight Heparin

The low molecular weight heparins (LMWHs) in common use are enoxaparin and dalteparin. The dose of enoxaparin (Clexane), the first LMWH to be introduced for prevention of DVT, is 40 mg subcutaneously daily; for the treatment of DVT or of PE, the dose is 1 mg/kg 12 hourly or 1.5 mg/kg daily.

The dose of dalteparin (Fragmin) for prevention of DVT is 2,500–5,000 units subcutaneous daily. For treatment of DVT and PE, the dose is 200 units/kg daily.

The LMWH has several pharmacokinetic and practical advantages over UFH. These are summarized as follows—

- Ease of use without need for routine monitoring of prothrombin time (PT) or INR.
- More predictable anticoagulant response.
- Standard dose apart from chronic renal failure (CRF) where the dose is reduced or halved, and morbid obesity where the dose is increased.
- Longer half-life, which permits once or twice daily-dosing.
- Facilitates earlier discharge and in some stable patients even home treatment.
- Lower risk of heparin-induced thrombocytopenia (HIT) or bleeding.
- Less binding to osteoblasts hence less osteopenia.

A meta-analysis of over 3,000 patients[15] who participated in DVT treatment studies showed that those receiving LMWH had lower mortality rates, less recurrence and suffered fewer complications including reduced HIT. All this was achieved at lower cost compared to UFH. A pivotal study by Levine[16] showed that enoxaparin, an LMWH administered twice daily reduced mean hospital stay from 6.5 to 1.1 days with fewer deaths and fewer bleeding complications. As a result of this and similar trials, the Food and Drug Administration (FDA) has approved enoxaparin (1 mg/kg twice a day) and tinzaparin (175 units/kg once daily) for outpatient or home treatment for

patients who present with symptomatic DVT with or without associated PE. As opposed to this data, there is as yet no data to suggest that outpatient treatment can be safely recommended in patients with PE alone. Whether LMWH or UFH is used, it serves as a bridge for five to seven days till anticoagulation with warfarin takes over.

Use of Xa Inhibitors

Fondaparinux is a factor Xa inhibitor which has been approved by the FDA for the prophylaxis of DVT and treatment of DVT and PE. The dose is 2.5–10 mg subcutaneously daily.

Oral Anticoagulation

Oral anticoagulation with warfarin is the mainstay of treatment and the dose is adjusted according to the PT. This is standardized by reporting results as the INR with a target INR of 2–3 being aimed for. In patients with recurrent PEs or underlying thrombophilic states the target INR is raised to 3–4. As mentioned earlier, current guidelines (2012)[14] recommend that warfarin is started early or the same day as heparin for treatment of both DVT/PE. Warfarin interacts with a number of commonly used drugs and even with the Vitamin K in green leafy vegetables resulting in wide fluctuations of INR. In addition, some patients (2–3% of the general population) have a genetic defect (polymorphisms in the cytochrome P450 CYP2C9), which makes them slow metabolizers and prone to major bleeding complications with even lower doses of warfarin. The current ACCP guidelines[14] on optimal duration of anticoagulation after a DVT/PE is ideally 3 months, if the patient had an underlying precipitating factor which is no longer applicable. In patients with a first episode of idiopathic DVT/PE in patients with a previous history of DVT/PE, in patients with active cancer, and in patients with high risk factors that are likely to persist, a 6–12 month initial period of anticoagulation is recommended. A study called the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial[17] showed that after 6 months of warfarin, lower intensity dosing, so as to target an INR of 1.5–2 resulted in a further significant reduction in the risk of recurrences by 64%. In patients who have documented antiphospholipid antibodies or an underlying thrombophilic state, indefinite anticoagulation therapy is recommended.

Recurrent Thrombosis[18,19]

The 5-year incidence of recurrent venous thromboembolism off anticoagulants is approximately 30%. Well-documented factors for recurrent thrombosis include an initial unprovoked DVT or PE, advancing age, male sex, race (higher in blacks), presence of active cancer, obesity, an elevated serum D-dimer prior to stopping warfarin or 2 months after stopping warfarin, and ongoing immobility.

Complications of warfarin include bleeding, skin necrosis, alopecia and rashes. When patients present with very high INRs as a result of warfarin, the majority will be asymptomatic even with INR values greater than 5. Most can be managed with fresh frozen plasma, if they are bleeding or low oral doses of vitamin K. The usual injectable dose of 10 mg of vitamin K will result in patients being resistant to further anticoagulation with warfarin for at least a week and hence should be avoided.

Warfarin is contraindicated in pregnancy as it can cause embryopathy and intracranial bleed in the fetus. LMWH can be used safely in pregnancy. As far as possible, warfarin should not be used with aspirin as major bleeds can occur even when the PT is in the therapeutic range.

Newer Oral Anticoagulants[14]

The two newer oral anticoagulants are dabigatran and rivaroxaban. Dabigatran is a direct thrombin inhibitor and is FDA-approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The dose is 150 mg twice daily if the creatinine clearance is greater than 30 mL/minute and 75 mg twice daily if the creatinine clearance is less than 30 mL/minute. Rivaroxaban is a factor-Xa inhibitor. It is FDA-approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The dose is 20 mg once daily if creatinine clearance is greater than 50 mL/minute and 15 mg once daily if the creatinine clearance is less than 50 mL/minute.

Bleeding is the main complication of anticoagulant therapy. Bleeding due to warfarin and other vitamin K antagonists can be countered by vitamin K given orally or intravenously (depending on the severity of the bleed and degree of rise in INR), as also by the administration of fresh frozen plasma. Bleeding caused by UFH can be countered by IV protamine and by fresh frozen plasma. The latter is also useful in patients with a dilutional coagulopathy. However, the newer anticoagulants including the Factor-Xa a inhibitors (e.g. fondaparinux, rivaroxaban) and the direct thrombin inhibitors (e.g. bivalirudin, dabigatran, lepuridin, argatroban) do not have a true antidote. In the setting of life-threatening bleeding, recombinant factor VIIa may enhance thrombin generation and has been used for a reversal effect against these anticoagulants. Table 2 gives recommended drugs used to counter the bleeding caused by various anticoagulants.

Thrombolysis[14,20]

Thrombolysis can be a potentially lifesaving measure in patients with massive PE. In patients with PE who present with hemodynamic compromise in particular with persistent hypotension, there is little doubt that thrombolysis is indicated and can dramatically lower mortality. *A more controversial decision is whether to extend the indications of thrombolysis to include patients with submassive PE.* These are patients with PE who are hemodynamically stable on a clinical examination, but who have evidence of RV dysfunction on echocardiography putting them at higher risk of a bad inhospital course. The presence of RV dysfunction is a warning sign that escalation of therapy may be required or that death

Table 2: Recommended drugs used for reversal of major bleeding caused by anticoagulants

Anticoagulant	*Reversal agent*	*Dose/timing*	*Special considerations*
LMWH: Enoxaparin (1 mg/kg SC for DVT/PE/MI) Dalteparin— For MI: 120 IU/kg of body weight SC every 12 hours For DVT/PE: 200 IU/kg total body weight (SC) once daily	1. Protamine 2. rVIIa for severe bleeding	1. 1 mg protamine IV for every 1 mg of enoxaparin or 100 U of dalteparin 2. rVIIa 50–90 mg/kg IV	Only partially reversed by protamine and may require repeated doses
Parenteral direct thrombin inhibitors— • Lepirudin • Bivalirudin • Desirudin • Argatroban	1. Cryoprecipitate 2. Antifibrinolytics 3. Desmopressin acetate	1. >10 U cryoprecipitate 2. ε-aminocaproic acid 0.1–1.5 g/kg IV over 30 minutes then 0.5–1 g/hr infusion 3. 0.3 mg/kg IV desmopressin acetate	Desmopressin can be repeated 8 hourly. Can develop hyponatremia and seizures
Factor-Xa inhibitor— • Fondaparinux • Rivoraxaban	1. rVIIa	In severe bleeds: 90 mg/kg IV	Immediate effect Duration of effect: 2–6 hours
Oral direct thrombin inhibitor— • Dabigatran	1. Oral charcoal 2. rVIIa	1. Given within 2 hours of last dose 2. rVIIa 60–90 mg/kg IV	Hemodialysis if kidney function deranged

may occur with a conservative "hands off" approach. Even though these patients may appear stable they may develop ensuing cardiopulmonary instability over the next 48 hours. Pooled data from four studies have shown that PE patients with RV dysfunction on ECHO have a ninefold higher risk of death than those with normal RV function.[21] Other biomarkers that also attempt to predict a subset of patients with higher mortality include Troponin T and I, which are sensitive markers of myocardial cell damage, and natriuretic peptides like B-type natriuretic peptide (BNP) and N-terminal probrain natriuretic peptide (NTpro-BNP), which are sensitive indicators of ventricular dysfunction. A limitation of both sets of biomarkers is that they have low positive predictive value but high negative predictive value with regard to death or poor outcome.

Thrombolytic agents, such as tissue plasminogen activator (TPA) act on plasminogen by cleaving the peptide bond between arginine at position 560 and valine at position 561, thereby converting plasminogen to plasmin and dissolving the embolus. They help dissolve the clot at source in the pulmonary vessels and perform a medical embolectomy, preventing the downward spiral into right heart failure. They may also help in dissolution of clot at its source in the pelvic and deep veins of the leg. The only FDA-approved regimen is alteplase 100 mg as a continuous infusion over 2 hours. However, streptokinase and urokinase-based regimens are probably equally efficacious and a lot cheaper. Streptokinase is administered as a loading dose of 250,000 U IV over 30 minutes and then 100,000 U/h for 24 hours. *Thrombolytics can be administered within a 2-week time window from the onset of PE and dramatic results have been reported in patients with massive PE, even in patients in shock and circulatory arrest.* The evidence of their role in submassive PE is also emerging, initially from small case studies in the 1960s, then from eight smaller randomized Level 2 studies in the next two decades and finally from the study by Konstantinides,[22] reported in the New England Journal of Medicine in 2002. In this landmark randomized, double-blind controlled study in 49 German centers, 256 patients who met strict inclusion criteria of submassive PE (no hemodynamic instability but RV dysfunction on echocardiography) were randomized to heparin plus recombinant-tissue plasminogen activator (r-TPA) or heparin plus placebo. Although this study could not demonstrate any difference in mortality between the two groups, the clinical deterioration was significantly higher in those that did not receive alteplase. The 30-day event-free survival was also significantly higher in the alteplase group so that patients not receiving alteplase were significantly more likely to need escalation of treatment.

On the basis of this study, many experts would consider using thrombolytic therapy in patients with submassive PE though admittedly there is no unanimity on this issue. Samuel Goldhaber a leading authority in the field remarks: "I believe on the basis of this trial that we should consider expanding the indications for thrombolysis to include this group of patients." However, as yet, the current ACCP guidelines advise thrombolysis only when massive thromboembolism is characterized by hemodynamic instability, in particular hypotension.

Complications of thrombolysis include bleeding but in a pooled analysis of 896 patients[23] enrolled in every PE thrombolysis study, the overall risk of intracranial bleed was

Box 5: Contraindications to anticoagulant therapy

- Recent major surgery/ocular surgery/neurosurgery
- Persistent diastolic BP >110 mm Hg
- Central nervous system hemorrhage
- Recent trauma/head injury
- Recent hemorrhagic cerebral infarct
- Gastrointestinal bleeding or other hemorrhagic diathesis; thrombocytopenia (<50,000/mm^3)
- Concomitant hepatic/renal failure or a coagulopathy from any cause

Box 6: Management of pulmonary embolism

- Anticoagulation with unfractionated or low molecular weight heparin
- Oral anticoagulation
- Thrombolysis
- Cardiorespiratory support
- Surgical embolectomy
- Catheter embolectomy

1.2%. It is best not to use heparin and thrombolytic therapy simultaneously as this can cause uncontrollable bleeding and death.

It is important to consider patients where anticoagulants and thrombolytic therapy are contraindicated (Box 5). The contraindications include a history of a very recent bleed, very recent major surgery, trauma, platelet count less than 50,000/mm^3, disordered coagulation (coagulopathy), whatever the reason, e.g. severe hepatic failure, renal failure. It is equally important to consider a situation where thrombolytic therapy has failed in a patient with massive embolism causing hypotension and hemodynamic instability.

In a patient with PE who is hemodynamically stable but in whom anticoagulation is contraindicated, it is advisable to insert an IVC filter. Anticoagulants can be given if the bleeding risk reduces or is controlled (as for example, the use of factor VIII in a patient with hemophilia + DVT/PE). In a patient with massive PE where anticoagulation and thrombolytic therapy administered through a peripheral vein is contraindicated, the use of streptokinase or TPA in a titrated dose locally through a pulmonary artery catheter inserted into the pulmonary artery has been tried by us in selected circumstances with success. It does not obviate completely the risk of major bleed but reduces it.

CARDIORESPIRATORY SUPPORT

This is imperative in major or massive PE. Shock should be promptly treated. An intravenous infusion of isoproterenol (1–2 mg in 500 mL dextrose) is very useful as it dilates the pulmonary vasculature. If possible, the patient should have a central venous line inserted and it is advisable to keep the CVP between 12 mm Hg and 14 mm Hg in order to ensure an adequate RV stroke volume. This is best achieved by infusing 500 mL dextran or haemaccel, which besides raising right atrial pressure, also expands the pulmonary vascular bed, and thereby reduces pulmonary vascular resistance. A disadvantage of isoprenaline is that is can increase an already existing tachycardia to a significant extent. Inotropic support with dopamine is essential. Dobutamine can also be used in addition to dopamine.

The use of digoxin is disappointing, but it may be used in a dose of 0.25 mg intravenously to start with, and repeated 6-hourly till a digitalizing dose of 1 mg is given over 24 hours. Oxygen is administered at 6–8 L/minute. Ventilator support is invariably required in the presence of acute cardiorespiratory failure. Morphine or pethidine is used for the relief of pain and/or restlessness.

SURGICAL EMBOLECTOMY[24]

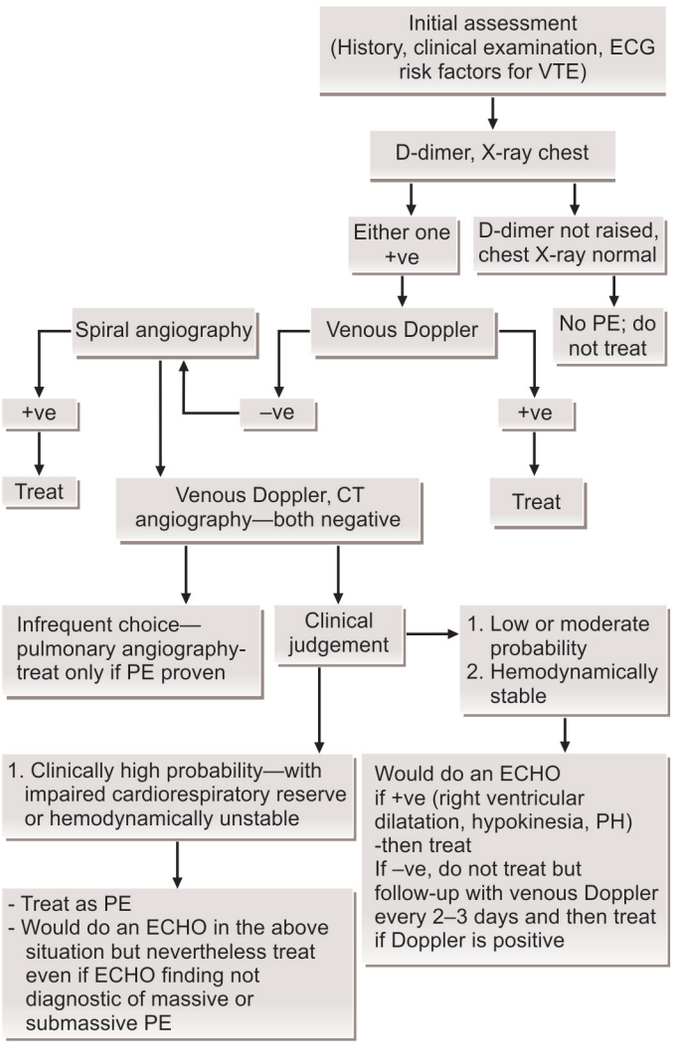
Open surgical embolectomy is the most effective procedure for emergent removal of large amounts of thrombus due to acute PE provided surgical expertise and experience are available. Surgery is especially useful in those in whom thrombolysis is contraindicated and who have not yet deteriorated to the point of cardiorespiratory arrest or shock. In this setting, when used in patients with anatomically extensive PE, and concomitant moderate to severe RV dysfunction, Goldhaber and colleagues[25] report impressive 89% survival rates. Impressive survival rates have been reported even in patients taken up in extremis after suffering cardiopulmonary arrest following massive PE.

Transvenous catheter embolectomy[26] in the catheter laboratory offers a less invasive alternative to open surgical embolectomy. A number of devices including the Greenfield embolectomy device, the Amplatz thrombectomy device, the Angiojet device and the hydrolyser thrombectomy catheter are available. The possibility that after catheter embolectomy a large fragmented clot could block the peripheral pulmonary circulation needs to be considered (Box 6).

PREVENTIVE MEASURES[27]

Prevention of venous thrombosis with the associated risk of PE is a major objective in the management of critically ill patients in the ICU. These patients often form a high-risk group as a consequence of bed rest, serious infections or trauma. Prevention of venous thrombosis in high-risk patients reduces morbidity. High-risk patients include the old and obese, those who are poorly mobile or are confined to bed, patients with myocardial infarction or a stroke, or those with atrial fibrillation and congestive heart failure. Postoperative patients are also at high risk, particularly after orthopedic surgery (particularly hip replacement or hip fracture), gynecological surgery and other major surgery. As

Flowchart 2: Algorithm for diagnostic work-up of pulmonary embolism


Initial assessment (History, clinical examination, ECG risk factors for VTE)
D-dimer, X-ray chest
Either one +ve
D-dimer not raised, chest X-ray normal
Spiral angiography
Venous Doppler
No PE; do not treat
+ve
–ve
+ve
Treat
Venous Doppler, CT angiography—both negative
Treat
Infrequent choice—pulmonary angiography-treat only if PE proven
Clinical judgement
1. Low or moderate probability
2. Hemodynamically stable
1. Clinically high probability—with impaired cardiorespiratory reserve or hemodynamically unstable
Would do an ECHO if +ve (right ventricular dilatation, hypokinesia, PH) -then treat
If –ve, do not treat but follow-up with venous Doppler every 2–3 days and then treat if Doppler is positive
- Treat as PE
- Would do an ECHO in the above situation but nevertheless treat even if ECHO finding not diagnostic of massive or submassive PE

Abbreviations: ECG, electrocardiogram; VTE, venous thromboembolism; PE, pulmonary embolism; PH, pulmonary hypertension.

Note: If venous Doppler negative, patient in shock or markedly hypotensive so that shift to the catheter lab risky, do a 2D ECHO. If positive for right ventiricular dysfunction + PH, treat as PE. If ECHO shows no RV dysfunction, search for some other cause of shock (Flowchart 1).

mentioned above, almost all patients in the ICU are at high risk for DVT. Critical illness from any cause itself constitutes a high risk. Should DVT prophylaxis with heparin be given to all critically ill patients? Each patient should be assessed individually, the risk of DVT being balanced against the risk of bleeding. Low molecular weight heparin (enoxaparin) in a dose of 40–60 mg subcutaneously daily offers good prophylaxis against DVT.

Compression stockings over lower limbs, movement of the lower limbs at the ankles and knees, pneumatic compression of the lower limbs, all help to prevent DVT. Any form of heparin is contraindicated in certain patients—as after trauma, following surgery on the brain and spinal cord, or in patients with an acute peptic ulcer or a bleeding diathesis. In this group one can only offer pneumatic compression of the lower limbs, with active and passive movements at the ankles and knees as prophylaxis.

Once venous thrombosis is detected LMWH in a dose of 40 or 60 mg of enoxaparin twice daily is given provided the above mentioned conditions are not present and there is no contraindication to the use of an anticoagulant. Warfarin is started on the same day as per the ACCP guidelines. It takes about a week of warfarin to take effect; heparin should be continued till such time as the INR is greater than 2. As mentioned earlier, a 6–12 month period of anticoagulants is advised after the first episode of DVT/PE for which there is no apparent cause, as also in patients with a previous history of DVT or PE, in patients with active cancer or in patients with high risk factors which cannot be removed. If anticoagulation is contraindicated, current guidelines advise the use of an IVC filter.

Box 7: Specific indications for insertion of an inferior vena caval filter

- Pulmonary embolism in patients in whom anticoagulants are absolutely contraindicated
- Recurrent thromboembolism in spite of adequate anticoagulation
- Hemodynamically unstable patients who have survived a massive embolism and where the possibility of recurrent embolism is strong
- Patients with septic pulmonary embolism
- Prophylaxis in high-risk patients

Transvenous Insertion of a Filter in the Inferior Vena Cava[28]

This is achieved by the placement of a filter in the IVC generally below the renal veins. The procedure is done by a vascular surgeon or an interventional radiologist through the transvenous route. The filter stops emboli from the lower limb or pelvic veins from reaching the lungs. Specific indications for vena caval interruption include the following (Box 7)—

- Pulmonary embolism in patients in whom anticoagulants are absolutely contraindicated—as in the neurosurgical patient, or in those with active bleeding.
- Recurrent thromboembolism in spite of adequate anticoagulation.
- Patients who have survived a massive embolism, but who are hemodynamically unstable, and in whom the risk of a fresh embolism is ever present.
- Patients with septic pulmonary embolism from thrombi in the lower limbs or pelvis, who have shown an unsatisfactory response after 48 hours of antibiotic plus anticoagulant therapy.
- Prophylaxis in high-risk patients, as in—
  - in extensive or progressive venous thrombosis.
  - in conjunction with catheter-based or surgical pulmonary embolectomy.
  - in patients with active cancer with extensive venous thrombosis of the pelvic or leg veins. Vena caval interruption in the last three groups should be accompanied by the use of heparin in the dosage recommended earlier.

Though IVC filters reduce the incidence of short-term embolic recurrence and reduce short-term (90 days) mortality, this benefit may be lost over a prolonged period of time. In fact, there appears to be a long-term increase in the incidence of venous thromboembolism following the use of IVC filters. For this very reason, retrievable IVC filters have been introduced. However, since these filters are endotheliazed at the point of vascular contact retrievability may be difficult after a lapse of time.

FAT EMBOLISM[29]

Fat embolism is a dramatic form of embolism, which occurs when neutral fat gains entry into the vascular system. The precipitating factor is a fracture of a long bone, the incidence increasing with multiple fractures. Fat embolism has been also noted to occur after orthopedic procedures and rarely following liposuction. It generally occurs 24–72 hours after these precipitating factors.

Pathophysiology

Fat embolism produces two effects—

1. Blockage of vessels by neutral fat.
2. The release of fatty acids due to the action of lipase on neutral fat. Liberated fatty acids cause a vasculitis with increased permeability of pulmonary, cerebral and other vascular beds.

Clinical Features

The clinical picture is characterized by the sudden onset of dyspnea, increasing hypoxemia and mental confusion. Acute lung injury or acute respiratory distress syndrome (ARDS) may occur as a result of increased permeability of pulmonary capillaries. Seizures or even focal neurological signs may be present. About 30–50% have petechiae on the skin, chiefly on the upper half of the body. There is no test, which is diagnostic of fat embolism. Fat may be present in the serum of patients with fat embolism.

Treatment

Treatment is generally supportive as no specific treatment has proved effective. Ventilatory support is invariably necessary. Use of corticosteroids in the prevention of fat embolism following an inciting factor is controversial.

AIR EMBOLISM[30]

An important form of nonthrombotic embolism is venous air embolism. The possibility of air embolism has increased with numerous invasive medical and surgical procedures in practice today. These include the use of central venous catheters, surgery on the neck, thorax, and use of positive pressure ventilation with high positive end expiratory pressure (PEEP). Two important causes are allowing a large bolus of air to enter a central vein by failing to notice that an infusion through the vein is over, and removing the central venous catheter in the sitting position.

Air bubbles enter the pulmonary vascular bed, blocking it; some bubbles go through microvascular pulmonary shunts to enter the systemic circulation.

Clinical Features

Clinical features include severe chest pain, dyspnea, hypoxia and syncope. Pulmonary edema and altered sensorium are observed if death has not already occurred. Symptoms are related to widespread blockage of the pulmonary circulation and of systemic capillaries by air and by platelet fibrin aggregates causing diffuse microthrombi.

Treatment

Treatment consists of—

- Placing the patient in the Trendelenburg position with the left side down.
- Removing air through a central venous catheter or direct needle aspiration, thereby promoting blood flow.
- Cardiorespiratory resuscitation.
- Promoting absorption of air by using 100% oxygen and when possible hyperbaric oxygen.

OTHER FORMS OF EMBOLISM

These include tumor embolism, septic thromboembolism, catheter embolism (a cut-off segment of a central venous catheter) and thrombotic complications caused by intravenous use of drugs meant to be taken orally, as is met with in some drug addicts.

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SECTION

8

Respiratory Problems Requiring Critical Care

- Acute Respiratory Failure in Adults
- Oxygen Therapy
- Airway Management
- Acute Exacerbation of Chronic Obstructive Pulmonary Disease
- Acute Lung Injury and Acute Respiratory Distress Syndrome
- Acute Severe Asthma
- Community-Acquired Pneumonias Requiring Critical Care
- Massive Hemoptysis
- Diseases of the Pleura in the Critically Ill
- Negative Pressure Pulmonary Edema

CHAPTER 28

Acute Respiratory Failure in Adults

GENERAL CONSIDERATIONS

Acute respiratory failure is an important and frequently encountered problem in intensive care units (ICUs) all over the world. The usual or traditional definition of respiratory failure is the inability of the respiratory system to maintain the normal homeostasis of arterial blood gases, so that the oxygen tension in arterial blood (PaO_2) is less than 60 mm Hg, and/or the carbon dioxide tension in arterial blood ($PaCO_2$) is 50 mm Hg or greater.

Respiratory failure may be acute or chronic depending on the onset and duration of the failure. An acute exacerbation may at times prevail over a background of chronic respiratory failure (acute on chronic failure).

Respiratory failure is mainly of two types: (1) Type I or hypoxic respiratory failure is due to a failure of oxygenation with a PaO_2 less than 60 mm Hg, (2) Type II or hypercapnic respiratory failure (ventilatory failure) is due to hypoventilation and is characterized by a $PaCO_2$ greater than 50 mm Hg. Hypoxemic and hypercapnic respiratory failure may both occur in the same patient. Some intensivists also consider Type III and Type IV failure.[1]

Type III respiratory failure is that occurring perioperatively and is largely due to basal atelectasis. Cardiothoracic surgery and/or major upper abdominal surgery splint the diaphragm and induce an abnormal mechanics of the abdominal muscles. These factors cause a fall in the functional residual capacity and an increase in the closing volume of the lungs. The end result is increasing atelectasis of the dependent alveoli, small lungs with a high diaphragm, respiratory distress and hypoxemia.[1]

Type IV respiratory failure is that associated with shock—a poorly functioning circulatory system with a low cardiac output is the main cause of hypoxemic failure in this situation. Both Type III and Type IV failure merely constitute hypoxemic failure or both hypoxemic and hypercapnic failure occurring against specific background conditions.

It is important to realize that the significance of the absolute value of arterial blood gas tensions varies from patient to patient. Thus, a fall in arterial PaO_2 from 95 mm Hg to even 70 mm Hg can be of ominous significance in a young man with rapidly evolving acute respiratory failure due to acute poliomyelitis or to any acute neuromuscular disease. This is because, (1) this fall constitutes a sharp or acute drop below the predicted range; (2) ventilatory failure due to acute poliomyelitis, acute neuromuscular disease, or to severe respiratory muscle fatigue from any cause, can produce a further precipitous fall in PaO_2 that can lead to death from severe hypoxia within a matter of a few hours or even minutes. Such a fall in PaO_2 does not necessarily occur in a graded or step-wise fashion. Under the above circumstances, to await a fall in PaO_2 to less than 55–60 mm Hg before realizing the gravity of the situation, can prove dangerous. Abnormal arterial blood gas tensions in a patient should therefore be judged in perspective with the natural history of the problem producing such an abnormality. *Disaster should be anticipated, and if possible prevented; it should never be awaited.*

The above traditional definition of acute respiratory failure evolved when measurements of arterial pH and arterial blood gas tensions were first introduced into clinical medicine. This definition is useful in that (1) it focuses attention on abnormalities of gas exchange due to disturbances in lung function; (2) it stresses the importance and need for a laboratory diagnosis of respiratory failure; (3) it emphasizes the difficulty and often the impossibility of either diagnosing

acute respiratory failure, or gauging its severity on clinical grounds. Yet, this traditional definition ignores the role of the cardiovascular system in gas exchange, and above all in oxygen transport to tissues. In a critical care setting, this is of particular concern. It is vital to look upon the circulatory and respiratory systems as a single inter-related unit whose purpose is to supply oxygen to the tissues.

A broad definition of respiration would be an exchange of oxygen and carbon dioxide between man and his environment.[2] It can be divided into the following sequential steps—

- *Ventilation*—in which an exchange of oxygen and carbon dioxide occurs between the lungs and the atmosphere.
- *Gas exchange*—this occurs across the alveolar-capillary membrane within the lungs, mixed venous blood being oxygenated, and carbon dioxide being removed during its transit through the lungs.
- *Gas transport*—the transport of oxygenated arterial blood to the tissues, and of venous blood (with a high carbon dioxide content), to the lungs.
- *Gas exchange within the tissues*—release of oxygen, oxygen uptake and utilization by the tissues, and release of carbon dioxide by the cells for transport back to the lungs.

In critical care medicine, it is a great advantage to look upon acute respiratory failure as an acute impairment of any one or more of the steps described above. We shall briefly consider (1) acute ventilatory failure; (2) acute failure in gas exchange or acute hypoxemic failure; (3) a combination of (1) and (2); (4) a failure of oxygen transport and (5) a failure of tissue oxygenation.

ACUTE VENTILATORY FAILURE

Definition

Acute ventilatory failure occurs when alveolar ventilation ($\dot{V}_A$) cannot adequately remove the carbon dioxide produced by cell metabolism, via the lungs.

Relation between PaO_2 and $PaCO_2$ in Ventilatory Failure

Ventilatory failure always results in a rise in $PaCO_2$ and a fall in PaO_2, and as mentioned earlier is also termed hypercapnic respiratory failure. The relation between PaO_2 and $PaCO_2$ is defined by the alveolar gas equation

$$P_AO_2 = PIO_2 - PaCO_2 \times \frac{1}{R}$$

where P_AO_2 is the alveolar oxygen tension, PIO_2 is the inspired oxygen tension corrected for water vapor, and R is the respiratory exchange ratio (see Section Basic Cardiorespiratory Physiology in the Intevsive Care Unit). Once the P_AO_2 is calculated from the above equation, the PaO_2 can be determined if the alveolar-arterial oxygen gradient is known. In ventilatory failure due to CNS causes or due to neuromuscular disease, the alveolar-arterial gradient is normal (i.e. 10–20 mm Hg), so that the PaO_2 is 10–20 mm Hg less than the P_AO_2. The oxygen-carbon dioxide diagram (Fig. 1) gives the value of P_AO_2 and PaO_2 for any given value of $PaCO_2$. The arterial blood gas tensions of oxygen and carbon dioxide fall on this line in pure or isolated ventilatory failure.

Physiopathology of Ventilatory Failure

The carbon dioxide produced by tissue metabolism ($\dot{V}CO_2$) is removed by the lungs. Normally, the alveolar carbon dioxide tension (P_ACO_2) and the arterial carbon dioxide tension ($PaCO_2$) are maintained around 40 mm Hg by adjusting $\dot{V}_A$ to balance the $\dot{V}CO_2$. Thus, an increase in the latter is met by a proportionate increase in $\dot{V}_A$. The relationship between P_ACO_2, $\dot{V}CO_2$ and $\dot{V}_A$, can be stated as follows—

$$P_ACO_2 = PaCO_2 = \frac{\dot{V}CO_2}{\dot{V}_A} \times \text{a constant (0.86)}$$

(See Chapter Basic Cardiorespiratory Physiology in the Intensive Care Unit).

$\dot{V}_A$ or the alveolar ventilation is the difference between minute ventilation ($\dot{V}_E$) and the physiological dead space ventilation

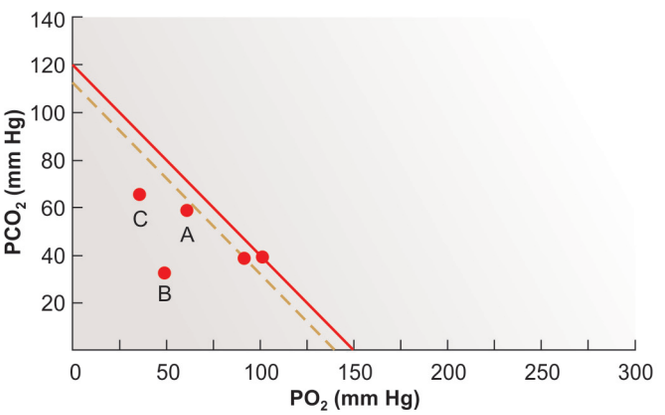


Fig. 1: O_2-CO_2 diagram. The continuous line represents the relation between alveolar PO_2 and alveolar PCO_2 with an RQ of 0.8 and when breathing air (PIO_2 = 149 mm Hg). The circle marked on this line represents the normal P_AO_2 and P_ACO_2. The broken line represents the normal relation between PaO_2 and P_ACO_2 ($PaCO_2$) when breathing air. It takes into consideration the slight venous admixture occurring in normal lungs so that the PaO_2 may be 10–15 mm less than P_AO_2. The circle marked on the broken line represents the normal PaO_2 and PCO_2. Points A, B and C illustrate blood gas readings in different types of respiratory failure: A. Ventilatory failure: $PaCO_2$ 60 mm Hg; PaO_2 65 mm Hg. The point falls on or is very close to the broken line. B. Hypoxemic failure: $PaCO_2$ 38 mm Hg; PaO_2 45 mm Hg. The point is markedly to the left of the broken line. The large alveolar-arterial gradient is chiefly due to a ventilation-perfusion imblance and/or an increase in the true venous admixture. C. Hypoxemic and ventilatory failure: $PaCO_2$ 70 mm Hg; PaO_2 30 mm Hg. Note high $PaCO_2$ indicating ventilatory failure and PaO_2 less than what can be predicted from the $PaCO_2$ reading. The point is again to the left of the broken line

Source: Udwadia FE. Diagnosis and Management of Acute Respiratory Failure, Mumbai: OUP; 1979.

($\dot{V}_D$) within the lungs—i.e. the ventilation that does not participate in gas exchange. The above equation can thus be rewritten:

$$P_ACO_2 = PaCO_2 = \frac{\dot{V}CO_2}{\dot{V}_E - \dot{V}_D}$$

Thus, a rise in $PaCO_2$ due to ventilatory or hypercapnic respiratory failure can occur under the following conditions: (1) A fall in $\dot{V}_A$ or alveolar ventilation—this could be due to (a) a fall in $\dot{V}_E$ or minute ventilation or to (b) a rise in physiological $\dot{V}_D$, without a concomitant increase in minute ventilation ($\dot{V}_E$); (2) A rise in carbon dioxide production ($\dot{V}CO_2$) without a proportionate increase in $\dot{V}_A$.

Important Causes of Acute Ventilatory or Hypercapnic Respiratory Failure in an Intensive Care Unit

- Hypoventilation in lungs which are normal to start with. This occurs in patients with a depressed ventilatory drive or in neuromuscular disease. A depressed ventilatory drive is observed in poisonings with narcotics, sedatives, antidepressants, coma from other causes, in head injuries, encephalitis, increased intracranial tension and other pathologies depressing the respiratory center. Important neuromuscular diseases causing hypoventilation include acute poliomyelitis, acute infective polyneuritis (Guillain-Barré syndrome), tetanus, myasthenia gravis, botulism and snake bite poisoning. Other causes of respiratory muscle weakness and/or decreased respiratory muscle endurance include severe myopathy, amyotrophic lateral sclerosis, polymyositis, critical illness polyneuropathy/myopathy, malnutrition, severe electrolyte disturbances, notably hypokalemia, hyperkalemia, hypomagnesemia, prolonged ventilator dependence, disorders of the phrenic nerve and respiratory muscle fatigue from any cause.
- Rarely hypoventilation can occur following large airways obstruction. In an ICU setting, this is chiefly observed in tracheal or subglottic stenosis, when an artificial airway has been in place for many weeks, or has been incorrectly managed. Upper airways obstruction with hypoventilation can also occur in children with acute epiglottitis, in obstructive sleep apnea, vocal cord paralysis, and foreign bodies including dentures, clots, secretions, soft tissue tumors or inflammation obstructing the upper airway.
- Poor expansion of the thoracic cage with ventilatory failure can occur following trauma to the thorax (as in flail chest), in patients who are severely obese, or have marked kyphoscoliosis, or in those with well-marked pleural disease (as in bilateral pleural effusion or pneumothorax).

It is important to realize that in most of the above-mentioned conditions, the lungs are normal to start with. However, if hypoventilation is not promptly recognized and correctly managed (and this is most important in hypoventilating comatose patients), secretions accumulate within the large and small airways producing areas of atelectasis. As a result of secondary changes within the lungs, gas exchange due to ventilation-perfusion imbalance is further impaired.

- Hypoventilation can also occur in lungs, which are abnormal. This is most frequently seen in severe airways obstruction—either acute severe asthma, or an acute crisis in chronic bronchitis emphysema. In these patients, hypoventilation is due to a decrease in $\dot{V}_E$, and/or an increase in physiological dead space. Extensive thromboembolic disease within the lungs can rarely produce a sufficient rise in $\dot{V}_D$, so as to cause a fall in $\dot{V}_A$. Severe late (almost terminal) stage restrictive disease can also be associated with hypoventilation and hypercapnic respiratory failure.
- Increase in carbon dioxide production, at times cannot be countered by an increase in $\dot{V}_A$. Marked increase in carbon dioxide production can occur in high fever, hypermetabolic critical illnesses, severe hyperthyroidism, frequent seizures and uncontrolled tetanus. In patients with respiratory muscle fatigue, or in those with mechanical limitations to breathing (as in severe COPD), $\dot{V}_A$ cannot keep pace with carbon dioxide production, and hypercapnic respiratory failure is observed. Hyperalimentation with increased caloric intake through carbohydrates or a high carbohydrate diet given by the enteral route also results in an increase in $\dot{V}CO_2$. An increase in $\dot{V}_A$ is imperative if this excess CO_2 is to be removed. In critically ill patients, carbon dioxide retention may occur as respiratory muscle fatigue may prevent a proportionate rise in $\dot{V}_A$ (see Section Nutritional Support in the Critically Ill Adult).

The important causes of hypercapnic respiratory failure in the ICU are listed in Box 1.

HYPOXEMIC RESPIRATORY FAILURE

Acute hypoxemic respiratory failure results from poor gas exchange of oxygen within the lungs leading to a low PaO_2. The $PaCO_2$ may be normal or even less than normal (Fig. 1).

Pathophysiology

The normal $\dot{V}_A$ is about 4–5 l and the normal perfusion (Q) is around 5 l, the $\dot{V}_A/Q$ ratio being approximately 0.8–1. Even in the normal lung, there are regional differences in ventilation and perfusion ratios, but by and large the ventilation and perfusion ratios are even and range from 0.8 to 1.2. For explanatory purposes, the lung can be compartmentalized into the following divisions—

- Alveoli with normal ventilation and perfusion—normal V/Q ratios.
- Alveoli with increase in ventilation-perfusion ratios, the V/Q ratios being greater than 1. The capillaries leaving these alveoli have a normal or slightly increased PaO_2 but a reduced $PaCO_2$.

Box 1: Important causes of hypercapnic respiratory failure in the ICU

1. Patients with normal lungs to start with (decrease in VE)—
   Depressed ventilatory drive—
   - Poisonings, e.g. narcotics, antidepressants, sedatives
   - Head injury, encephalitis, increase in intracranial tension
   - Coma from any cause

   Neuromuscular diseases—
   - Acute poliomyelitis, acute infective polyneuritis, polymyositis and critical care neuromyopathy
   - Myopathy, amyotropic lateral sclerosis
   - Tetanus, myasthenia gravis and botulism
   - Snake bite poisoning
   - Respiratory muscle weakness or fatigue from any cause

   Large airways obstruction—
   - Tracheal/subglottic stenosis, obstructive sleep apnea, vocal cord paralysis and foreign bodies

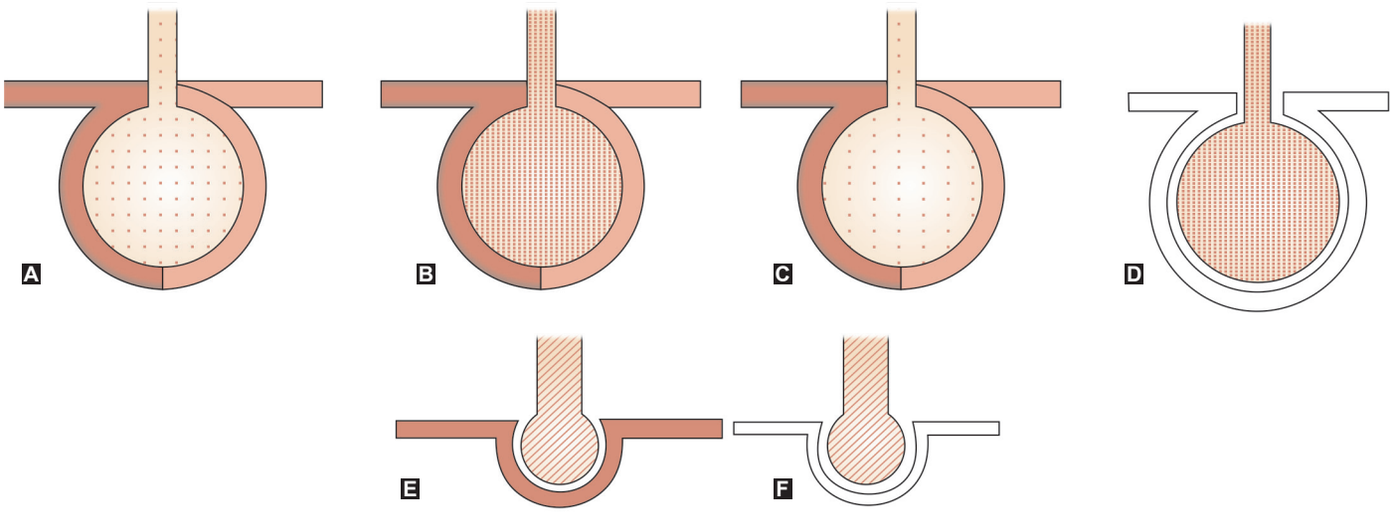
   Poor expansion of the thoracic cage (failure of the Bellows)—
   - Trauma (flail chest), severe obesity, kyphoscoliosis, extensive eschar after burns, pleural effusion and pneumothorax
2. Patients with abnormal lungs (decrease in $\dot{V}_E$ and/or increase in $\dot{V}_D$)—
   - Acute severe bronchial asthma
   - Acute crisis in chronic bronchitis, emphysema
   - Extensive thromboembolic disease
   - Severe terminal stage restrictive lung disease
3. Patients with increased production of CO_2—
   - High fever, hypermetabolic critical illnesses
   - Frequent seizures, uncontrolled tetanus
   - Hyperalimentation with increased carbohydrate intake

- Alveoli with a decrease in ventilation-perfusion ratios; blood after perfusing these alveoli has a lowered PaO_2 and an increased $PaCO_2$. The lower the V/Q ratio, the lower the PaO_2 of the blood leaving these alveoli.
- Alveoli that are ventilated, but have no perfusion. The V/Q ratio is infinity, and such alveoli contribute significantly to increased physiological dead space.
- Alveoli which are atelectatic but continue to be perfused. These alveoli contribute to a right to left shunt within the lungs. The blood leaving the alveoli has the same PaO_2 as mixed venous blood, i.e. 40 mm Hg.
- Alveoli which are neither ventilated nor perfused. These are resting alveoli, and probably come into physiological action only when ventilatory or respiratory demands increase (Figs 2A to F).

Acute hypoxemic respiratory failure occurs when: (1) there is a ventilation-perfusion mismatch characterized predominantly by low ventilation-perfusion ratios in the lungs; (2) there is a significant increase in the right to left shunt due to perfusion of atelectatic alveoli; (3) both the above factors are present; (4) there is a marked decrease in diffusion of oxygen across the alveolar capillary membrane.

Low Ventilation-Perfusion (V/Q) Ratios

Alveoli, which have a perfusion in excess of ventilation (i.e. low $\dot{V}_A/Q$ ratios), will have a reduced P_AO_2, and therefore a reduced PaO_2, as well as a reduced oxygen content of blood leaving the alveoli. When the poorly oxygenated blood mixes with the blood perfusing the alveoli that have $\dot{V}_A$ which is normal in proportion to the perfusion, or $\dot{V}_A$ even in excess of the perfusion, the resultant blood stream has a lower oxygen



Figs 2A to F: Various gas exchange units in the lung (A) Normal unit alveoli with normal V/Q ratios; (B) Hyperventilated unit-alveoli with increase in V/Q ratios (>1); (C) Hypoventilated unit-alveoli with decrease in V/Q ratios; (D) Dead space unit-alveoli are ventilated, but have no perfusion; (E) Shunt unit-alveoli are atelectatic but have good perfusion; (F) Silent unit-alveoli are neither ventilated nor perfused

Source: Modified from Udwadia FE. Diagnosis and Management of Acute Respiratory Failure. Mumbai: OUP; 1979.

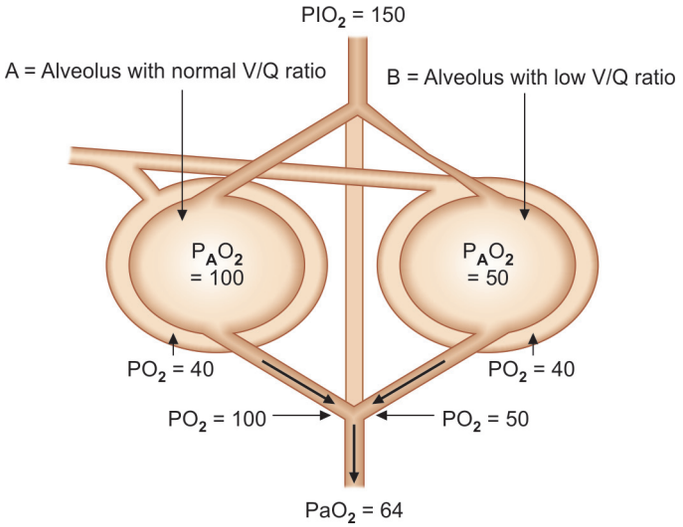


Fig. 3: The PaO_2 of blood leaving A (alveolus with normal V/Q ratio) is normal; the PaO_2 of blood leaving B (alveolus with reduced V/Q ratio) is reduced. When this poorly oxygenated blood mixes with well-oxygenated blood from alveoli with normal or high V/Q ratios, the resultant PaO_2 is still lower than normal. This shows that increased V/Q ratios in some alveoli cannot compensate for markedly lowered V/Q ratios in other alveoli

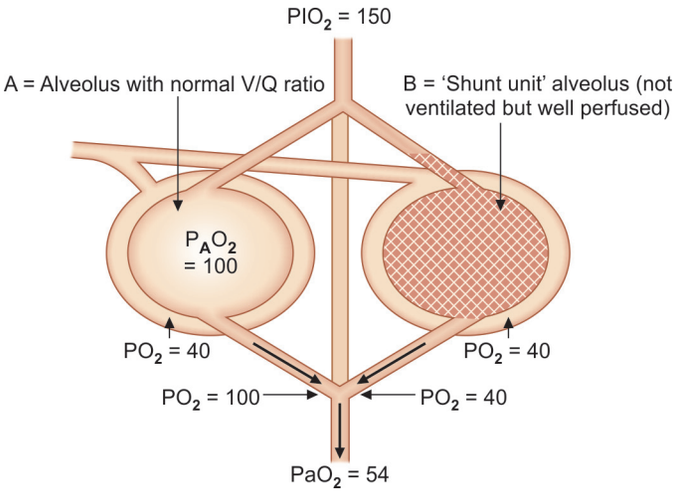

PIO_2 = 150
A = Alveolus with normal V/Q ratio
B = 'Shunt unit' alveolus (not ventilated but well perfused)
P_AO_2 = 100
PO_2 = 40
PO_2 = 40
PO_2 = 100
PO_2 = 40
PaO_2 = 54

Fig. 4: The PaO_2 of blood leaving A (alveolus with normal V/Q ratio) is normal. The mixed venous blood perfusing; B (shunt unit alveolus) is not oxygenated at all. When this blood mixes with well-oxygenated blood perfusing a normal alveolus, the resultant PaO_2 is still very low

content and a lowered PaO_2. Increased V/Q ratios in some alveoli cannot compensate for sharply lowered V/Q ratios in other alveoli. After all, the oxygen saturation of arterial blood in the presence of normal V/Q ratios is close to 100%. A further increase in the V/Q ratio may increase both the P_AO_2 and the PaO_2, but because of the plateau-shape of the upper part of the oxygen-hemoglobin dissociation curve, there will be no appreciable increase in oxygen saturation or content of blood leaving such alveoli. This is illustrated in Figure 3.

Increase in Right to Left Shunt within the Lungs

A shunt refers to the proportion or fraction of venous blood that enters the systemic arteries without coming into contact with gas exchanging areas of the lungs. The present discussion is not concerned with right to left shunts in the heart or the larger vessels due to congenital defects or anomalies. Right to left shunts within the lungs due to perfusion of atelectatic alveoli constitute the most important cause of refractory acute hypoxemic respiratory failure. It is to be remembered that there is a small right to left shunt even in normal lungs. This is because of bronchial venous blood draining directly through pulmonary veins into the left atrium, and a small amount of coronary venous blood that drains via the Thebesian veins directly into the left ventricle. The normal shunt averages not more than 5%. In patients with a right to left shunt due to perfusion of atelectatic alveoli, the shunt fraction may be as high as 30–50%. The higher the right to left shunt within the lungs, the greater the degree of hypoxemia, and lower the PaO_2.

The effect of a right to left shunt within the lungs is illustrated in Figure 4.

Combination of Low V/Q Ratios and Increased Shunt

Most lung diseases causing acute respiratory failure are characterized by a pathology in which there are areas of low V/Q ratios, high V/Q ratios and increase in the right to left shunt. Patients in whom disturbance in gas exchange is predominantly due to an increase in the shunt have the gravest prognosis.

Impairment in Diffusion of Oxygen

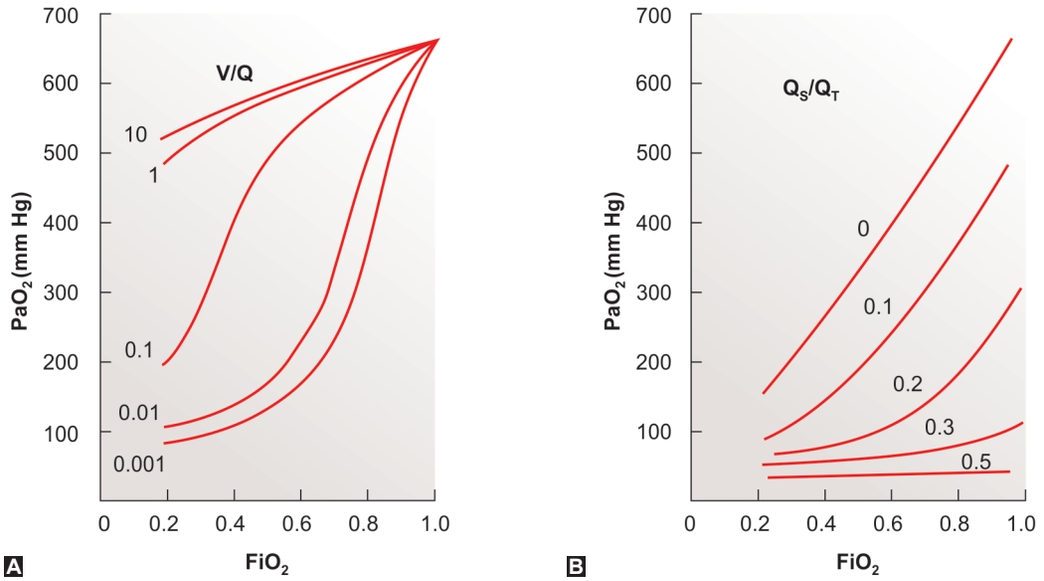
A diffusion abnormality does exist in several lung diseases, but it almost never is the chief cause of a low PaO_2 at rest. All patients with diffusion abnormalities have regional variations in compliance resulting in uneven and low ventilation-perfusion ratios.

Effect of an Increasing Inspired Oxygen Content (FiO_2) on V/Q Abnormalities

Increase in the FiO_2 rapidly produces an increase in the PaO_2 and the oxygen content of blood leaving the alveoli with low V/Q ratios. The hypoxemia of acute respiratory failure in patients with low V/Q ratios is thus easily corrected. The improvement in PaO_2 depends upon the degree of perfusion to areas with poor ventilation. Except where the V/Q ratios are extremely low, a satisfactory PaO_2 of about 60 mm Hg, with an oxygen saturation of 90% is achieved by using a FiO_2 of less than 0.6. Even in alveoli with extremely low V/Q ratios, as long as there is some ventilation present, an FiO_2 of 100% will always produce a marked increase in the PaO_2 of blood leaving such alveoli. This is illustrated in Figure 5A.

Effect of an Increased FiO_2 on the Shunt

It is obvious that the treatment of hypoxemia due to a severe right to left shunt within the lungs is difficult, because increasing the



Figs 5A and B: (A) PaO_2 improves with increasing FiO_2 in patients with a V/Q mismatch. When the FiO_2 is increased to 1 (100%), the PaO_2 reaches 600 mm Hg even if the V/Q ratio is very low. (B) Note that with increase in Q_S/Q_T beyond 0.3, increasing the FiO_2 has little or no effect on the PaO_2

Source: Albert RK. Physiology and management of failure of arterial oxygenation. In: Fallat RJ, Luce JM (Eds). Cardiopulmonary Critical Care Management (Clinics in Critical Care Medicine). Elsevier Inc.; 1988. pp. 37-59.

FiO_2 improves the oxygen content to a very slight extent. The greater the shunt, the poorer the response in PaO_2 to a rise in FiO_2 (Fig. 5B). Fortunately, acute hypoxemic respiratory failure solely due to a marked increase in the right to left shunt within the lungs is rare. Even in patients with severe acute respiratory distress syndrome (ARDS), though there are many areas of shunt, which do not respond to an increase in FiO_2, there are some areas of V/Q mismatch which respond to such an increase.

Clinical Problems Causing Acute Hypoxemic Respiratory Failure

These can be broadly divided into three groups—

1. Those characterized chiefly by airways obstruction causing uneven ventilation and V/Q inequalities—an acute crisis in chronic bronchitis emphysema, and acute severe asthma are classic examples. In some of these patients, there is an element of acute ventilatory failure in addition to hypoxemic respiratory failure. This is due to mechanical limitations, which prevent increased ventilatory demands from being adequately met, to alveolar hypoventilation consequent to a marked increase in physiological $\dot{V}_D$, or to a diminished respiratory drive. One or more of these factors may contribute to an associated ventilatory failure.
2. *Restrictive lung diseases* Examples of these include acute pulmonary edema, acute interstitial disease, acute pulmonary infections, acute lung injury (ARDS) and major atelectasis within the lungs.
3. *Acute thromboembolic lung disease* This is characterized by V/Q inequalities and increase in the dead space resulting in acute hypoxemic respiratory failure.

Box 2: Important causes of acute hypoxemic respiratory failure

- Obstructive airways disease—
  - Acute crisis in chronic bronchitis, emphysema
  - Acute severe bronchial asthma
- Restrictive lung disease—
  - Acute pulmonary edema; acute interstitial disease
  - Acute pulmonary infection
  - Acute lung injury [acute respiratory distress syndrome (ARDS)]
  - Major pulmonary atelectasis
- Trauma to the chest
- Acute thromboembolic lung disease

The important causes of acute hypoxemic respiratory failure are listed in Box 2.

A COMBINATION OF ACUTE VENTILATORY AND HYPOXEMIC RESPIRATORY FAILURE

This is seen in intensive care medicine in the following groups of patients—

1. Acute severe asthma.
2. Acute or chronic respiratory failure due to a respiratory crisis in patients with chronic airways obstruction (COPD).
3. Muscle fatigue involving muscles of respiration in patients with acute respiratory failure due to severe lung disease.
4. Advanced or late stage interstitial lung disease.
5. Severe pulmonary thromboembolism.
6. Trauma to the chest (Flail chest).

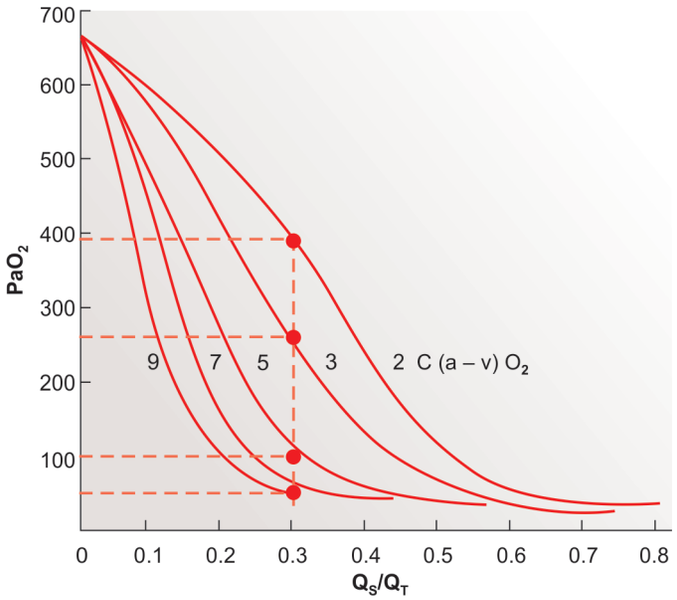


Fig. 6: Dependence of PaO_2, on the oxygen extraction C (a-v) and the shunt fraction. If the shunt fraction is 30%, the PaO_2, varies from 100 mm Hg to 400 mm Hg, as the C (a-v) O_2 narrows. The patient may have a high PaO_2, if he has a high cardiac output and a decreased C (a-v) O_2 of 3, even if his shunt fraction is as high as 0.3. However, if the patient's oxygen consumption increases without a corresponding increase in the cardiac output, the C (a-v) O_2 widens to 9, and the PaO_2, falls to 50 mm Hg

Source: Albert RK. Physiology and management of failure of arterial oxygenation. In: Fallat RJ, Luce JM (Eds). Cardiopulmonary Critical Care Management (Clinics in Critical Care Medicine). Elsevier Inc.; 1988. pp. 37-59.

FAILURE OF OXYGEN TRANSPORT

A satisfactory gas exchange at the alveolar level must be accompanied by an adequate transport of oxygenated blood to the tissues. This requires an adequate cardiac output, a normal oxygen content of arterial blood and good tissue perfusion (see Section Basic Cardiorespiratory Physiology in the Intensive Care Unit). A low output state or shock from any cause can also indirectly lower the PaO_2 in the following ways—

- A low cardiac output results in increased oxygen extraction from the blood by the tissues. This leads to a fall in the mixed venous oxygen content (PvO_2). The lowered PvO_2 in the mixed venous blood reaching the alveoli will lead to a lowered PaO_2. This can be even more marked if the cardiac output falls in a patient who already has a right to left shunt within the lungs (Fig. 6).
- A low output state leads to a low pressure of perfused blood in the pulmonary vessels; perfusion is more in the dependent alveoli of the lungs. This results in an increase in the physiological dead space involving non-dependent alveoli, and to low V/Q ratios within the dependent alveoli of the lungs, thereby contributing to a fall in PaO_2.
- Respiratory muscle fatigue is an important factor in low output states. Hypotension and shock lead to poor perfusion of respiratory muscles and quick, easy fatigability. Respiratory muscle fatigue can cause hypoventilation, can increase ventilation-perfusion inequalities, and can thereby further reduce the PaO_2.

RESPIRATORY MUSCLE FATIGUE

The importance and role of muscle fatigue in acute respiratory failure in critically ill patients cannot be overemphasized and is best considered at this stage. As with other muscle groups in the body, excessive work performed by the muscles of respiration leads to fatigue.[1,3] Increasing fatigue results in increasingly poor function and hypoventilation; ultimately the patient literally stops breathing. Increasing respiratory fatigue explains the abrupt stoppage of breathing with resulting disaster, in patients with acute severe asthma, or in patients with a very low pulmonary compliance due to acute alveolar edema. Difficulties in weaning patients off ventilator support are also frequently related to respiratory muscle fatigue brought on by the inability to cope with the work of breathing.

The second major factor predisposing to respiratory muscle fatigue is the gravity or critical nature of an illness. The more critically ill the patient, the easier and quicker does fatigue arise in respiratory muscles. Tachypnea and an unstable circulation, hypotension with poor perfusion of the respiratory muscles, electrolyte disturbances, probably all play a role in muscle fatigue in these individuals.

The clinical recognition of respiratory muscle fatigue is difficult and may occasionally be impossible to detect till the patient very nearly has a respiratory arrest. A voiced complaint by an ill patient that he or she is tired and cannot continue to breathe for long should always be taken seriously, particularly in a patient with severe airways obstruction. Tachypnea with a rate greater than 35/minute, always predisposes to fatigue, particularly in obese individuals or very ill patients. Poor chest excursions, irregular breathing and above all apneic spells, all point to fatigued respiratory muscles. Respiratory alternans, in which intercostal muscle and diaphragmatic contractions alternate, is also observed at times. Fatigued muscles also occasionally cause a paradoxical respiratory movement, with the lower part of the chest and the upper abdomen being drawn in, instead of being pushed out during inspiration.

Objective measurements are also of use. As a rough guide, spontaneous breathing cannot be easily sustained if the effort involved in each spontaneous breath is less than one-third of the maximal respiratory effort that can be achieved.[3-5] The maximum inspiratory pressure (MIP) is a good guide to the respiratory muscle power. An MIP of less than 30 cm H_2O generally denotes muscle fatigue. Similarly, a tidal volume (VT)(measured by a Wright's spirometer) of less than 300 mL, or a vital capacity (VC) less than three times the VT, suggests respiratory muscle fatigue *under appropriate clinical conditions*. A minute ventilation greater than 10–12 L/minute is difficult to sustain indefinitely in critically ill individuals, and often ultimately leads to hypoventilation from respiratory muscle fatigue. The objective measurements stated above when judged against an appropriate clinical background can give only indirect evidence of probable respiratory muscle

Box 3: Features of respiratory muscle fatigue

- Complaint of fatigue in relation to breathing
- Respiratory rate greater than 35 breaths per minute
- Poor chest excursions, irregular breathing and apneic spells
- Respiratory alternans, paradoxical respiratory movements
- Maximum inspiratory pressure (MIP) less than 30 cm H_2O
- Tidal volume (VT) <300 mL; vital capacity (VC) <3 x TV; minute ventilation (VM) >10–12 L/min

fatigue. It has to be admitted that unequivocal direct evidence of contractile fatigue has not yet been demonstrated. The major determinants of respiratory muscle fatigue are inspiratory muscle strength, mean inspiratory pressure and the duration of inspiration, which when combined form the tension time index (TTI).[6] However, interpretation of the TTI is difficult and often misleading.[6] Recent work suggests that the magnetic stimulation of the phrenic nerve (a procedure far less painful than electrical stimulation) can detect diaphragmatic fatigue; and by measuring changes in the esophageal twitch pressure, can also detect rib-cage muscle fatigue.[7,8] Magnetic stimulation of the phrenic nerve is however a research procedure not generally performed in critical care units. It is best to act on the premise that respiratory muscles (particularly if they are weak) can, like other skeletal muscles, experience fatigue if subjected to excessive work for a prolonged period of time.

The clinical features of respiratory muscle fatigue are listed in Box 3.

Respiratory muscle fatigue causing or contributing to acute respiratory failure should be managed by resting the respiratory muscles by mechanical ventilation. During the period of rest, the acutely depleted glycogen stores of the respiratory muscles are replenished, and lactic acid and other metabolites associated with muscle fatigue are washed out.[9-11] Aminophylline is believed to preserve muscle strength and contraction of the diaphragm; however, it is doubtful if this drug has a clinical role in patients with severe respiratory muscle fatigue.

FAILURE OF OXYGEN UPTAKE

Despite good ventilation, normal exchange of blood gases at the alveolar level and good oxygen transport, oxygen uptake may be deficient at the tissue level. The main purpose of the cardiorespiratory system is then defeated. Thus, cyanide poisoning is characterized by an arrest of intracellular respiration due to the inactivation of an intracellular enzyme, cytochrome oxidase. The patient with cyanide poisoning has a normal PaO_2, SaO_2, CaO_2 and oxygen transport, but cannot utilize oxygen at the tissue level. Blood after perfusing tissues shows severe lactic acidosis and has a high PvO_2 and $S\dot{v}O_2$. The patient literally dies of strangulation or hypoxia at the tissue level.

The most important clinical problem associated with failure of oxygen uptake is septic shock, often associated with ARDS [this is discussed under Sepsis and Septic Shock and Acute Lung Injury (ARDS)]. To many physicians, it may seem inappropriate to consider failure of oxygen uptake by tissues in acute respiratory failure. Yet in critical care medicine, it is ultimately the oxygen supply to, and oxygen uptake by tissues (in particular tissues of vital organs), which are of crucial importance. In the final analysis, acute cardiorespiratory failure is a failure to adequately oxygenate the tissues.

CLINICAL FEATURES OF ACUTE RESPIRATORY FAILURE

In the presence of a background disease known to cause acute respiratory failure, the only sure way to diagnose the latter is by estimating the arterial blood gases. One should never rely only on clinical features to diagnose acute respiratory failure. Clinical features may however be present. These include the presence of disease known to cause acute respiratory failure, and the features associated with hypoxia and hypercapnia. Many, though not all patients, also show respiratory distress.

Hypoxia

Hypoxia is the basic underlying feature in every patient with acute hypoxemic respiratory failure. Increasing hypoxia depresses cell function, induces metabolic acidosis, and if marked and unrelieved leads to cellular death. It may be impossible to detect hypoxia on clinical grounds in critically ill patients. The only sure way of detecting hypoxia is by measuring the arterial PaO_2. The importance of this fact cannot be overemphasized.

The only pathognomonic manifestation of hypoxia is central cyanosis. Nevertheless, well-marked arterial hypoxemia may exist in the absence of clinical cyanosis, so that to await the development of cyanosis before diagnosing acute respiratory failure, is to court disaster. Cyanosis can only be clinically evident if the mean capillary concentration of reduced hemoglobin exceeds 5 g/dL. It is evident that a patient with severe anemia (Hb <7 g/dL), may die of severe arterial hypoxemia before cyanosis can become clinically manifest. A hypermetabolic state with a hyperdynamic circulation characterized by a quick blood flow through the peripheries also renders the clinical recognition of cyanosis difficult. The presence of anemia together with a quickened circulatory flow therefore constitute a formidable combination, which prevents the clinical appearance of cyanosis in spite of marked hypoxia.

Mental confusion, restlessness and acute anxiety are early manifestations of hypoxia. The ghastly pitfall of dubbing the anxiety and restlessness of early hypoxia in acute respiratory failure as functional, should be guarded against.

Compensatory Mechanisms Induced by Hypoxia

Hypoxia triggers compensatory mechanisms, which are easily recognized and are therefore of diagnostic value. The main compensatory mechanism is sympathetic stimulation

which causes tachycardia and hypertension. Increase in the respiratory rate is another compensatory mechanism produced by stimulation of the chemoreceptors in the carotid body and aorta. Increase in respiratory rate will not occur if the respiratory center is markedly depressed, or if there is weakness or paralysis of the respiratory muscles. However, tachycardia and hypertension are important signs of hypoxia. They should be sought for, and their significance recognized in situations that can lead to acute respiratory failure. These signs depend on the integrity of the sympathetic nervous system. In the old and feeble, in diabetics with a neuropathy involving the sympathetic nerves, or in patients who have received drugs affecting the autonomic nervous system, sympathetic response to hypoxia may be absent or feeble. With severe increasing hypoxia, the clinical hallmarks are progressive bradycardia, hypotension, lactic acid acidosis, arrhythmias, circulatory failure and death.

The myocardium has no oxygen reserve so that hypoxia depresses myocardial function, and increases ectopic irritability. Bradycardia and hypotension result from the direct depressant effect of hypoxia on the myocardium. Arrhythmias arise due to increased ectopic irritability. Atrial flutter and fibrillation are often observed; severe hypoxia ultimately results in ventricular tachycardia, fibrillation and arrest.

Hypercapnia

Hypercapnia may also be impossible to detect on clinical grounds. The $PaCO_2$ should therefore always be estimated in any disease, which can conceivably produce carbon dioxide retention.

Carbon dioxide has a local depressant effect on the cardiovascular system. It thus produces generalized vasodilatation except in the pulmonary circulation, which may be vasoconstricted. Generalized vasodilatation manifests as cutaneous flushing, warmth, sweating and a bounding pulse.

The depressant effect of carbon dioxide on the central nervous system leads to confusion, disturbance in behavior, a reversal in the sleep rhythm, and increasing drowsiness that may lead to deep coma (carbon dioxide narcosis). Carbon dioxide narcosis is an important metabolic cause of coma, and can be often missed if the $PaCO_2$ is not measured. Wing flap tremors of the outstretched hands are often observed with CO_2 retention. They are indistinguishable from those observed in hepatic failure. Wing flap tremors are not consistently present. At times, even a slight rise in the $PaCO_2$ induces wing flap tremors; at other times, a marked rise in $PaCO_2$ may not be associated with flaps. However, increasing levels of $PaCO_2$ produce increasing disturbance of consciousness. Marked confusion and drowsiness occur by the time $PaCO_2$ rises to between 80–100 mm Hg, and the patient is generally unconscious when the $PaCO_2$ is well over 100 mm Hg. Coma in CO_2 narcosis is associated with loss of the deep reflexes and urinary incontinence. The plantars are generally not elicitable or are flexor; rarely they may be extensor.

Table 1: Important clinical features of hypoxia and hypercapnia

Hypoxia	*Hypercapnia*
Cyanosis	Flushing, warmth, sweating, bounding pulse
Mental changes, restlessness, anxiety	Headache, wing flap tremors
Tachycardia, hypertension	Drowsiness, confusion, coma
Rhythm disturbances	Muscle twitching, seizures, papilledema
Metabolic acidosis	
Bradycardia, hypotension, circulatory failure, when hypoxia is marked	

High levels of $PaCO_2$ can produce headache, muscle twitchings, seizures and papilledema. The combination of drowsiness, headache and papilledema closely simulate an intracranial tumor.

An increasing $PaCO_2$ stimulates the respiratory center, producing an increase in the respiratory rate and V_T. Nevertheless, a depressed center or a center with a reduced or absent sensitivity to increasing $PaCO_2$, will not permit an increased respiratory drive to materialize.

Hypercapnia also produces a central stimulation of the sympathetic nervous system, resulting in tachycardia and hypertension. The pattern of symptoms in a patient will depend on the balance between the depressant action on the cardiovascular system, and the stimulant effects on the sympathetic nervous system.

Respiratory Distress or Dyspnea

Many patients in acute respiratory failure are uncomfortably aware of a difficulty in breathing. This unpleasant awareness of respiration and difficulty in breathing is termed dyspnea. Dyspnea is a subjective phenomenon, and its correlation with the degree of respiratory failure is difficult. In fact, breathlessness and respiratory failure are not synonymous. Many patients, who are breathless, are not in respiratory failure, and a number of patients in respiratory failure are not breathless. Nevertheless, in a patient with chronic lung disease, increasing impairment of lung function and increasing respiratory failure, are invariably associated with increasing dyspnea.

The important clinical features of hypoxia and hypercapnia are listed in Table 1.

AN ELECTIVE DIAGNOSTIC ASSESSMENT IN ACUTE RESPIRATORY FAILURE (BOX 4)

Acute respiratory failure may occur with a suddenness and severity that warrants immediate efforts toward resuscitation. Nevertheless, whenever time and the patient's condition permit, an elective diagnostic work-up is necessary. This is done with three objectives in mind—

Box 4: Elective diagnostic assessment in acute respiratory failure

1. Establish cause and estimate tempo or rate of progression of problem causing acute respiratory failure

Detailed history, for example, of poisoning, of symptoms suggestive of important diseases causing acute respiratory failure

Physical examination—

- Check for features of hypoxia, hypercapnia, patency of airways
- Meticulous examination of the cardiovascular and respiratory systems

Routine investigations—

- Arterial blood gas analysis
- Other tests, for example, complete blood count (CBC), serum biochemistry, chest X-ray

Special investigations (only if deemed necessary)—

- Monitoring of central venous pressure
- Monitoring of pulmonary artery pressures, cardiac output, and shunt fraction by use of the Swan-Ganz catheter

2. Determine nature of disturbance in respiratory physiology

Evaluate if ventilation is adequate—

- Hypoventilation if $PaCO_2$ >48–50 mm Hg
- Hyperventilation if $PaCO_2$ <35 mm Hg

Evaluate the following possible physiological abnormalities underlying a low PaO_2 —

- Hypoventilation
- Mismatched V/Q ratios
- Increased right to left shunt within lungs
- Impaired diffusion

Assess if there is increase in physiological dead space

Evaluate if work of breathing is increased

Check for evidence of respiratory muscle fatigue

Check if oxygen transport and tissue oxygenation are adequate

1. To establish the cause of acute respiratory failure.
2. To determine the nature of disturbance in respiratory physiology.
3. To estimate in so far as is possible, the tempo or the rate of progression of the disease, and the problems or complications likely to occur in the immediate or near future.

History

This is of great importance in evaluating the nature and tempo of the problem causing acute respiratory failure. Special stress should be laid on a history of poisoning, or of symptoms suggestive of important diseases known to cause acute respiratory failure—e.g. acute infective polyneuritis, airways obstruction, intracranial and other central nervous system lesions, myasthenia gravis and cardiopulmonary diseases.

Physical Examination

A thorough physical examination is mandatory. The following points are of special importance—

- An examination particularly oriented towards detection of clinical situations that lead to acute respiratory failure.
- A careful examination of the respiratory system. The importance of carefully counting the respiratory rate over a minute cannot be overemphasized. Polyphonic wheezes denote airways obstruction. The rhythm and pattern of breathing are also of importance. In ventilatory failure due to neuromuscular disease, the ability to hold the breath in inspiration and count numbers serially should be noted. Ordinarily, one can easily count up to 30. Inability to count up to 20 or more is a sure sign of marked neuromuscular weakness or of respiratory muscle fatigue. Crackles over the lungs point to pulmonary edema or to interstitial lung disease. Tight airways obstruction need not be accompanied by an auscultatory wheeze, particularly in patients with a lazy respiratory center and with carbon dioxide retention. A forced expiratory effort may bring out a wheeze in such patients, provided they are not obtunded, and can follow commands.
- The cardiopulmonary system should be regarded as a single or interrelated unit, responsible for supplying oxygen to the tissues. A careful examination of the heart and the circulatory system is therefore as important as an examination of the respiratory system. The pulse, arterial blood pressure, central venous pressure, body temperature, moisture and color of the skin, and color of the mucosal surfaces and the nails are all of importance.
- Specific features of hypoxia and hypercapnia should be looked out for; their absence however should never lull the clinician into a false sense of complacency.

Routine Investigations

Arterial blood gas analysis (pH, PaO_2, $PaCO_2$) is absolutely mandatory to confirm a clinical suspicion of acute respiratory failure, or for that matter, to establish a diagnosis even when no clinical suspicion of acute respiratory failure is entertained.

Other routine laboratory investigations include a complete blood count with a packed cell volume (PCV), urine analysis, serum electrolytes, other relevant biochemical parameters and a chest X-ray.

Special Investigational Procedures

In difficult cases, e.g. in the management of acute lung injury (ARDS), or in severe fulminant tetanus, or in patients with acute respiratory failure and shock, special procedures are of use not only in the diagnostic evaluation, but also in the management. These investigational procedures include measurements of the central venous pressure through a central line, and of the arterial blood pressure through a catheter in the radial artery. A Swan-Ganz catheter may need to be inserted to measure the pulmonary artery pressure, the pulmonary capillary wedge pressure, and the cardiac output by the thermodilution technique. The Swan-Ganz catheter is also necessary to measure the mixed venous oxygen

content, and thereby determine the shunt fraction or venous admixture within the lungs. *Invasive procedures outlined above should never be done routinely, but only in problem patients where further information is necessary not only for a complete evaluation, but also for management*. Iatrogenic problems with invasive procedures can be significantly frequent and dangerous. Every good critical care unit must be able to confidently state that the value of an invasive procedure undertaken in a given case clearly outweighs the potential iatrogenic hazards involved. Fortunately, the high cost of the Swan-Ganz catheter, prohibits its frequent use in our country.

As mentioned earlier, the basic disturbance in respiratory physiology must be determined. The following standard questions should therefore be asked, and their answers determined—

- *Is ventilation adequate?* The only certain way to determine this is to measure the $PaCO_2$; a $PaCO_2$ >48–50 mm Hg indicates hypoventilation, while a $PaCO_2$ <35 mm Hg, hyperventilation.
- *What is the physiological abnormality underlying a low PaO_2?* A lowered PaO_2 is an essential feature of acute respiratory failure, and this could be due to—
  - *A reduced FiO_2*, which could arise only at high altitudes.
  - *Hypoventilation* If so, the decreased PaO_2 is related to the increased $PaCO_2$, as determined by the O_2-CO_2 diagram, or the alveolar-oxygen equation stated earlier. The alveolar-arterial gradient remains normal (between 10 mm Hg and 20 mm Hg) in patients in whom a lowered PaO_2 is due to hypoventilation.
  - *Mismatched ventilation-perfusion ratios* Unequal V/Q ratios with an overall reduction in the ratio produce a lowered PaO_2. When plotted on the O_2-CO_2 diagram, the point lies well to the left of the line representing the O_2-CO_2 relationship. The alveolar-arterial gradient is therefore increased (>20 mm Hg).
    Hypoxia due to mismatched V/Q ratios is easily corrected by administering an increased FiO_2. Thus oxygen administered through nasal prongs or catheters, or via an orofacial mask at a rate of 4–6 L/minute suffices to produce a substantial rise in the PaO_2, and a fall in the alveolar-arterial oxygen gradient. However, if the V/Q ratios are very low, a FiO_2 of 0.6 or more is necessary to produce a significant rise in the PaO_2. 100% oxygen always abolishes hypoxia (and a low PaO_2) resulting from even the most severe ventilation-perfusion inequalities.
  - Increased right to left shunt within the lungs, i.e. an increase in the true venous admixture. A significant right to left shunt is suspected clinically when even a high FiO_2 fails to result in a significant rise in the PaO_2. The exact degree of right to left shunt can be calculated by the shunt equation as follows—

$$\frac{Q_S}{Q_T} = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}$$

Box 5: Causes of low PaO_2 unrelated to abnormal gas exchange within the lungs

- Low PvO_2 due to decreased cardiac output, or increased oxygen extraction by peripheral tissues due to increased tissue metabolism
- Severe anemia (Hb <7 g/dL)
- Shift of oxygen dissociation curve to the left as in alkalosis, hypothermia, lowered $PaCO_2$, decreased 2, 3-diphosphoglycerate in red blood cells (RBCs)

The CvO_2 can be obtained by sampling the mixed venous blood through a Swan-Ganz catheter. The Q_S/Q_T ratio determined on 20% oxygen gives the overall physiological shunt, i.e. the true venous admixture plus the shunt effect produced by alveoli with low ventilation-perfusion ratios. The Q_S/Q_T ratio determined on 100% oxygen inspired over 20 minutes, abolishes the shunt effect produced by alveoli with low ventilation-perfusion ratios, and gives a value of the true venous admixture, or the actual right to left shunt due to perfusion of totally atelectatic alveoli.

- The degree of true venous admixture can also be roughly estimated by noting the alveolar-arterial oxygen gradient when the patient is on 100% oxygen for 20 minutes. If the alveolar-arterial gradient exceeds 100 mm Hg, it points to the presence of a right to left shunt. The greater the alveolar-arterial gradient on 100% oxygen, the greater the degree of shunt (see Chapter Basic Cardiorespiratory Physiology in the Intensive Care Unit).
- *Impaired diffusion* Though interstitial and alveolar disease might cause impaired oxygen diffusion across the alveolar capillary membrane, the contribution of this impairment to a lowered PaO_2 is not as important in clinical medicine as the effect of ventilation-perfusion inequalities. What is more, an increased FiO_2 can counter any fall in PaO_2 related to reduced oxygen diffusion.

It is extremely important to realize that a lowered PaO_2 could be due to, or influenced by factors other than an abnormal gas exchange within the lungs (Box 5). Factors unrelated to gas exchange, which can lower the arterial PaO_2 include—

- *A low PvO_2* due to a lowered cardiac output, or to increased oxygen extraction by the peripheral tissues because of increased tissue metabolism.
- *Severe anemia* This is initially compensated by an increase in cardiac output. When this does not occur, or when the hemoglobin falls below 7 g/dL, there is a significant fall in the PvO_2 and the mixed venous oxygen content, which ultimately causes a fall in the PaO_2.
- *A shift in the oxygen dissociation curve to the left* as in alkalosis, hypothermia, lowered $PaCO_2$, or a decrease in the 2,3-diphosphoglycerate in the red blood cells. A leftward shift of the oxygen dissociation curve leads to a fall in the PaO_2 for an equivalent degree of oxygen saturation,

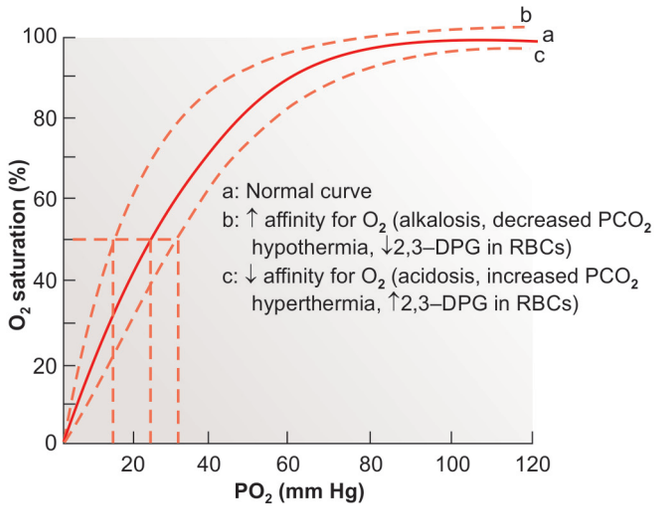


Fig. 7: Normal oxygen-dissociation curve (a), and curve shifted to left (b), and right (c). Curve (b) indicates increased affinity for oxygen, while curve (c) denotes decreased affinity for oxygen. Note that for an equivalent degree of O_2 saturation, the PO_2, level fails with a leftward shift in the oxygen dissociation curve

as compared to a normal oxygen dissociation curve. This is even more marked when there is a sudden shift of this curve from right to left (Fig. 7).

A clear evaluation of extrapulmonary factors is of great importance in critically ill patients, as it improves patient management and care.

- *Is there an increase in the physiological dead space?* An increase in the physiological dead space immediately points to uneven ventilation-perfusion ratios and to regional hyperinflation. An indirect method of assessing dead space is by determining the minute ventilation required to maintain a normal $PaCO_2$. The volume of ventilation exceeding the predicted value, is a measure of increased ventilatory requirements, and is generally due to an increase in the physiological dead space, provided that an increase in the $\dot{V}CO_2$ (i.e. CO_2 produced by tissue metabolism) can be excluded.

If the PCO_2 of mixed expired gas can be determined, then the dead space volume ($\dot{V}_D$), in relation to the V_T is given by the following equation—

$$\frac{\dot{V}_D}{V_T} = \frac{PaCO_2 - PECO_2}{PaCO_2}$$

where $PECO_2$ is the PCO_2 of mixed expired gas.

In patients on ventilator support, Levesque and Rosenberg[12] have devised a rapid and easy method of calculating dead space in relation to V_T. Assuming a normal $\dot{V}_D/V_T$ of 0.3 and a normal $PaCO_2$ of 40 mm Hg,

$$\frac{\dot{V}_D}{V_T} = \frac{V_M \times PaCO_2}{\dot{V}_E} \times \frac{0.3}{40}$$

where V_M is the measured minute ventilation, and $\dot{V}_E$ is the expected minute ventilation from a Radford nomogram.

- *Is the work of breathing increased?* Increased airways obstruction and/or a decrease in the compliance of the lungs or the thoracic wall, or both, result in an increased work of breathing. Though both can be gauged clinically, an exact estimation of airways resistance, and/or of pulmonary compliance in a critically ill patient with acute respiratory failure, is convenient only when the patient is on ventilator support. However, peak flow readings in patients with obvious airways obstruction, particularly when serial readings are measured, are of considerable value in estimating the degree and progress of airways obstruction (see Chapter Acute Severe Asthma).
- *Is there evidence of respiratory muscle fatigue?* Muscle fatigue is determined by the strength of the respiratory muscles and the load of breathing on respiration. Weak muscles and an increased load or work of breathing predispose to muscle fatigue. A clinical evaluation of muscle fatigue and simple bedside objective measurements to assess the possible presence and degree of respiratory muscle fatigue has already been discussed earlier.
- *Is oxygen transport satisfactory?* An adequate cardiac output is necessary for oxygenated arterial blood to reach the tissues. Cardiac output can be clinically gauged by noting the pulse, arterial blood pressure, skin temperature, urine output per hour, the presence or absence of lactic acid acidosis and the presence or absence of dysfunction of major organ systems. In difficult problems, the cardiac output needs to be measured by the thermodilution technique. When the cardiac output is low, oxygen transport can be enhanced by measures to increase the cardiac output. This chiefly is through manipulation of factors that determine cardiac output, namely the preload, cardiac contractility, the afterload, and the rate and rhythm of the heart (see Section Basic Cardiorespiratory Physiology in the Intensive Care Unit).

A normal hemoglobin is also necessary for an adequate oxygen content; a hemoglobin of 9–10 g/dL is generally aimed at in critically ill patients with acute respiratory failure.

- *Is tissue oxygenation adequate?* Good tissue oxygenation is the ultimate aim of restored cardiopulmonary function. There is a great deal more that we need to know about assessment of tissue oxygenation. An increase in lactate levels in the blood is a sure sign of poor tissue oxygenation. In septic shock and in ARDS, utilization of oxygen by the tissues may be inadequate even in the presence of a normal oxygen transport and supply.

MANAGEMENT OF ACUTE RESPIRATORY FAILURE (BOX 6)

There are a number of diseases producing acute respiratory failure for which there is no specific cure. The patient then needs respiratory care and support till such time as the

Box 6: Management of acute respiratory failure

- Maintenance of clear airway—
  - Clear secretions—
    - Liquefy secretions
    - Promote cough—good physiotherapy
    - Suctioning of secretions
    - Use of an airway—oropharyngeal airway, other airways, endotracheal intubation/tracheostomy
- Maintenance of adequate ventilation—
  - Artificial ventilation with an AMBU bag in an emergency till mechanical ventilator support is organized
  - Use of respiratory stimulants (in rare situations)
- Use of oxygen
- Treat cause of acute respiratory failure whenever possible
- Use mechanical ventilator support if cause cannot be treated, or if patient hypoxic or hypercapnic despite above measures

disease resolves. There are other diseases producing acute respiratory failure for which specific therapy is available. Prompt diagnosis and specific treatment in such instances can quickly reverse respiratory failure. The general principles involved in the management of acute respiratory failure include: (1) maintenance of a clear airway; (2) maintenance of adequate ventilation; (3) use of oxygen; (4) treating the cause of acute respiratory failure, in so far as this is possible and (5) the use of mechanical ventilation when indicated—if the cause of acute respiratory failure cannot be treated, or if the patient is hypoxic or hypercapnic despite above measures.

Maintenance of a Clear Airway

Obstruction of the airways due to retained secretions, mucus plugs or foreign matter (invariably food particles), worsen respiratory failure. Secretions obstructing airways can lead to hypoventilation with a further fall in the PaO_2. Mucus plugs within airways contribute to uneven and poor distribution of inspired gas to the alveoli within the lungs, and also produce areas of atelectasis. Uneven ventilation accentuates V/Q inequalities, whilst increasing areas of atelectasis worsen or produce a right to left shunt within the lungs. The net effect is increasing hypoxia and worsening respiratory failure. Undrained secretions or mucus plugs also form a nidus for infection, which may ultimately lead to pneumonia or bronchopneumonia. Maintaining a clear airway is, therefore, vital. This is often lost sight of in a comatose patient who may have normal lungs to start with, but who develops a quickly worsening respiratory failure due to undrained secretions plugging the airways.

Methods to Clear Secretions

- *Liquefy secretions* Undrained secretions can dry and form crusts, which obstruct the airways. Such crusted secretions can be removed only with great difficulty; therefore drying of secretions should be prevented, and their liquefaction promoted by—
  - Proper hydration of the patient, if necessary with intravenous fluids. A severely ill, distressed and breathless patient generally does not drink enough water on his own.
  - *Humidification of inspired gas* This is of utmost importance when the nasal and upper respiratory passages are bypassed, and the patient is breathing through an endotracheal or tracheostomy tube. Lack of humidification in such patients besides causing drying and crusting of secretions in the trachea, the large and the small airways, can also result in inspissated secretions that block the endotracheal or tracheostomy tube with disastrous consequences.
  - *Use of N Saline* 2–3 mL of N saline can be instilled through the endotracheal or tracheostomy tube to liquefy thick secretions which can then be aspirated. Acetylcysteine is also a good liquefactant of inspissated mucus, but is a strong irritant. It can produce severe bronchospasm even in a dose as small as 0.5 mL. The drug can also markedly increase the volume of secretions in the tracheobronchial tree, necessitating very frequent suction. We use this drug very rarely in our unit.
- *Promotion of cough* Cough, in a patient with acute respiratory failure should always be assisted and promoted and never suppressed. When pain prevents cough (as after thoracic, open heart or upper abdominal surgery, or in crush injuries), analgesics need to be given, taking care to use a dose that does not produce respiratory depression. Physiotherapy is vital to enable secretions to be brought up and coughed out. The patient may need to be postured to drain his secretions. In critically ill patients who retain secretions within the respiratory tract, good physiotherapy often spells the difference between survival and death.
- *Removal of secretions by suction* When secretions gather in the mouth and the upper respiratory passages, and the patient is too ill to spit or cough them out, frequent suction should be done to keep the upper airways patent, and to prevent the possibility of aspiration of the secretions into the lungs. Secretions around the larynx can be sucked with the aid of indirect laryngoscopy. Suction stimulates cough in an obtunded patient, and this is of added help. It is important never to roughly touch or hit the tip of the catheter to the pharynx or larynx during suctioning, as this can traumatize the pharyngeal or laryngeal mucosa, induce bleeding and sloughing, and further worsen the problem of maintaining a clear airway. The tip of the suction catheter should lie on the posterior portion of the tongue, preferably not touching the pharynx during suctioning. The floor and sides of the mouth should be suctioned; the nasal cavity and the pharynx can also be conveniently suctioned through a catheter inserted through the nares.
- *Endotracheal intubation* (also see Chapter Airway Management). If the upper airway cannot be kept clear

and open by the methods indicated above, or by the use of a simple oropharyngeal or nasopharyngeal airway, the patient should be intubated. Endotracheal intubation is an invaluable aid to maintain a clear airway as it allows easy access to secretions in the trachea and the large airways. The indications for endotracheal intubation and a tracheostomy as also the management of these artificial airways have been discussed in the Chapter Airway Management.

The main indication for endotracheal intubation is upper airways obstruction and the inability of the patient to handle upper respiratory secretions. The latter feature is frequently observed in unconscious patients, and is invariably so in comatose patients. It also occurs when the cough reflex is poor or the patient is just too ill or feeble to cough. Paralysis of the palate and pharynx will also prevent the patient from handling his upper respiratory secretions because of difficulty in swallowing. This could lead to aspiration of accumulated secretions, as also to aspiration of regurgitated stomach contents. The four common conditions in critical care medicine wherein an endotracheal tube serves to maintain an open airway are poisonings by respiratory depressants, cerebrovascular accidents, coma from any cause and following major surgery. Endotracheal intubation is also indicated when the patient is to be put on mechanical ventilator support.

Maintenance of Adequate Ventilation

Artificial Ventilation

When respiration is feeble, or the patient is apneic, immediate resuscitation is aimed at ensuring adequate ventilation. Initially, mouth-to-mouth respiration may be necessary, followed within seconds by a mask fitted to an AMBU or anesthetic bag, fed with 100% oxygen. This should be quickly followed by endotracheal intubation, mechanical ventilation being carried out either through an AMBU bag or by a mechanical ventilator.

Use of Respiratory Stimulants in Acute Respiratory Failure

The role of respiratory stimulants in acute respiratory failure in ICUs is very limited and to many non-existent. No respiratory stimulant acts specifically and solely on the respiratory center; all such drugs in addition to stimulating the respiratory center, also act as analeptics, in that they awaken the patient, and thereby enable him to ventilate and cough better. In fact, almost certainly the analeptic effect is clinically more important than the specific stimulating effect on the respiratory center. Good physiotherapy should always be given during an analeptic phase, so that secretions within the lungs are mobilized, and either coughed up or removed through suction. Unfortunately, all respiratory stimulants and analeptics frequently produce vomiting as a side effect, and if the dose is large, or the drug is administered rapidly, localized twitchings or generalized seizures can result. If alveolar hypoventilation due to a depressed respiratory center is sufficiently severe to produce well-marked hypoxia and hypercapnia, it is far better to use noninvasive ventilation or to intubate and ventilate the patient, rather than waste time in administering respiratory stimulants. We have stopped using respiratory stimulants in our unit.

Perhaps the only valid use of respiratory stimulants is (1) to tide over a critical period in a patient with acute respiratory failure, while he awaits transfer to an ICU; (2) in patients with hopelessly crippling chronic obstructive pulmonary disease (COPD) who on balance, are not given ventilator support. Respiratory stimulants could then be tried along with the other far more important conservative measures.

The respiratory stimulant with probably the least side effects is doxapram. It is given intravenously at a rate of 1–3 mg/minute, and can be continued till a maximum dose of 600 mg is reached.[13] The risk of seizures is low with doxapram. The infusion can however cause hypertension and cardiac arrhythmias as the drug can stimulate the release of epinephrine from the adrenals. It should therefore be avoided in hypertensive patients, and in those with ischemic heart disease.

Use of Oxygen

The prompt administration of oxygen is crucial in the management of acute respiratory failure. This is considered in a separate section.

Treatment of the Cause of Acute Respiratory Failure Whenever Possible

Treatment is individualized depending upon the etiological factor operating in a patient. The following examples are illustrative and worthy of mention—

- *Treatment of infection* This is the commonest cause that precipitates acute respiratory failure in patients with chronic lung disease. Infection can also occur later as a complication in the natural history of acute respiratory failure due to other causes.
- Removal of air in a tension pneumothorax, and tapping of a massive unilateral pleural effusion or moderate sized bilateral effusions.
- Removal of a foreign body obstructing the larynx, trachea, or a large bronchus.
- Expanding an atelectatic lobe or lung with physiotherapy or bronchoscopic suction.
- Use of prostigmine in myasthenia gravis and of antivenin in snake bite poisoning.
- Use of naloxone in narcotic poisonings.
- Use of nebulized beta-2 agonists, intravenous aminophylline, and oral or intravenous corticosteroids in acute severe asthma.

There are many situations where the cause of acute respiratory failure cannot be promptly treated. This particularly holds true for the numerous conditions, which produce

ARDS, severe tetanus, severe head injuries and other CNS problems and poisonings due to sedatives and tranquillizers. The doctor in charge of the ICU has then to rely on the general principles of management outlined above, till such time as the illness causing acute respiratory failure resolves over a period of time.

Mechanical Ventilation

When well-marked and in particular life-threatening hypoxia and/or hypercapnia are uncorrected by the general principles stated above, the patient needs mechanical ventilator support to aid in more effective gas exchange within the lungs. This is dealt with in a separate chapter.

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CHAPTER 29

Oxygen Therapy

INTRODUCTION

Oxygen is used as therapy in most critically ill patients under intensive care. It can be lifesaving in acute respiratory failure, yet can be lethal if incorrectly used. Oxygen administration aims at increasing the P_AO_2 and thereby the PaO_2 and the oxygen saturation of arterial blood (SaO_2). Except in some instances, it is enough to aim at a saturation of 90%; oxygen saturation less than 90% generally corresponds to a PaO_2 less than 60 mm Hg, and denotes the presence of moderate hypoxia. A moderate degree of hypoxia disturbs normal cell metabolism and function; marked hypoxia results in cellular death. A PaO_2 less than 20 mm Hg for a significant length of time generally produces brain death; yet a PaO_2 a little above 30 mm Hg probably maintains adequate cell function if the blood flow is adequate.

We have no means of accurately assessing cell function, and there is no doubt that the sensitivity of certain tissues (such as the brain and the heart) to oxygen lack is far greater as compared to other tissues (e.g. skin and muscle). It is possible that even minor degrees of hypoxia which are easily tolerated in a young healthy individual, might pose problems in critically ill individuals, or in those with a poor coronary circulation, or with impaired cerebral blood flow due to diffuse cerebrovascular disease. It is important to relieve hypoxia of even mild intensity in all such critically ill patients, and preferably aim at oxygen saturation well over 90%.

INDICATIONS FOR OXYGEN THERAPY

Hypoxia is the prime indication for oxygen administration. Dramatic relief with oxygen therapy is chiefly observed when arterial hypoxemia (i.e. a low PaO_2) is due to a low P_AO_2 or ventilation-perfusion mismatch within the lungs. Relief of hypoxia in such patients often brings in its wake three other effects—

1. Decrease in the work of breathing. Hypoxia often causes increased ventilatory work and relief of hypoxia is often followed by a decrease in the work of breathing.
2. Decrease in myocardial work. The heart and circulatory systems are frequently involved in compensatory responses to hypoxia; once the hypoxia is reversed, these compensatory responses abate and the work of the myocardium is reduced.
3. Improvement in cell function involving various organ systems of the body is a welcome aspect of adequate oxygenation to the tissues.

Indications for oxygen therapy are given in Box 1.

Hypoxemia[1]

In an acute setting, hypoxemia (low SaO_2 with a low PaO_2) is the most important and most frequent indication for administering oxygen. These patients (particularly when hypoxemia is due to a respiratory problem) benefit the most with oxygen therapy. The following situations are included in this group—

- Cardiopulmonary or respiratory arrest. Administration of oxygen is of vital importance, but is of no avail unless the patient is simultaneously ventilated and cardiac resuscitation (in a cardiac arrest) is successfully performed.
- Anesthetic error or accident.
- Hypoventilation from any cause.
- Respiratory diseases characterized by ventilation-perfusion mismatch, with or without impaired diffusion across the alveolar capillary membrane. These include severe chronic obstructive pulmonary disease (COPD), acute severe

Box 1: Indications for oxygen therapy

- Hypoxemia—
  - Cardiopulmonary or respiratory arrest
  - Anesthetic error or accident
  - Hypoventilation from any cause
  - Respiratory diseases characterized by ventilation-perfusion mismatch, with or without impaired diffusion across the alveolar capillary membrane
- Respiratory distress with a respiratory rate >24/min
- Pneumothorax
- Myocardial infarction and unstable angina
- Decreased oxygen content of arterial blood—
  - Severe anemia
  - Carbon monoxide poisoning
  - Methemoglobinemia, sulfhemoglobinemia
- Decreased transport of oxygen with impaired perfusion of tissues—
  - Shock from any cause
  - Left ventricular failure
  - Cardiac arrhythmias causing hemodynamic instability
  - Cardiac arrest
- Poor uptake or utilization of oxygen in tissues
- Postoperative states

asthma, as also interstitial lung disease. The commonest cause of hypoxemia in clinical medicine is a ventilation-perfusion mismatch. Patients who have this underlying abnormality benefit the most with oxygen therapy. In fact, if in a hypoxemic patient administration of oxygen leads to a sharp rise in the PaO_2 and SaO_2, the underlying cause of hypoxemia can be confidently attributed to a ventilation-perfusion mismatch or to hypoventilation.

- Respiratory diseases associated with an increase in the right to left shunt within the lungs as in acute respiratory distress syndrome (ARDS), atelectasis, and pneumonia. When there is a true right to left shunt in the lungs (desaturated blood pumped by the right ventricle perfusing totally atelectatic alveoli), there can be no relief of hypoxemia following use of oxygen. However, even in well-marked ARDS there also exists some degree of ventilation-perfusion abnormality with ventilation/perfusion (V/Q) ratios less than 1. Some degree of relief may therefore be expected. The larger the right to left shunt the lesser the relief. Patients with shunts greater than 30% may show little relief from administered oxygen.
- Respiratory distress with a respiratory rate greater than 24/minute is an indication for oxygen therapy as per American College of Chest Physicians (ACCP), National Heart, Lung and Blood Institute (NHLBI) Conference on Oxygen therapy.[2]

Pneumothorax

High concentration of pure oxygen [fraction of inspired oxygen (FiO_2) 60%] has been shown to quicken resolution of a pneumothorax. This is related to an increase of pressure in the gases within the pleural space following use of pure oxygen at a high FiO_2, so that the increased pressure gradient between the air in the pleural space and the surrounding tissues accelerates the absorption of nitrogen from the pleural space.

Myocardial Infarction and Unstable Angina[3]

The American Heart Association (AHA) guidelines for Advanced Cardiac Life Support (ACLS) recommend the use of supplemental oxygen in all patients with the acute coronary syndrome regardless of the presence or absence of hypoxemia. Though undoubtedly useful in hypoxemia (which may be present in the acute stage of a myocardial infarct), the administration of oxygen in patients who are normoxic is not based on convincing data.

Decreased Oxygen Content of Arterial Blood (Other Than That Caused by a Decrease in PaO_2)

- Severe anemia.
- Carbon monoxide (CO) poisoning.
- Methemoglobinemia, sulfhemoglobinemia.

The use of high concentration of oxygen is useful but limited in scope as the PaO_2 is generally normal in this group; it is the oxygen content which is low.

Chronic anemia is generally well tolerated. In acute severe anemia, use of high-flow oxygen through a non-rebreathing mask is of help, in addition to blood transfusions.

In carbon monoxide poisoning, CO combines avidly with hemoglobin (Hb) to form a stable compound carboxyhemoglobin (COHb), thereby sharply reducing the oxygen-carrying capacity of the blood. Management consists of administering oxygen at 10 L/minute through a tight-fitting reservoir mask. The use of close to 100% oxygen provides one-third of the body requirement of oxygen through the extra oxygen dissolved in plasma. It also reduces the half-life of COHb from 10 hours to 4 hours. Hyperbaric oxygen can further reduce the half-life to 20 minutes and can provide enough oxygen in solution to fully take care of the oxygen requirements of the body.

In acute severe methemoglobinemia, inhalation of a high concentration of oxygen is a useful temporary measure (for reasons stated above) till the methemoglobenemia is reversed.

Decreased Transport of Oxygen with Impaired Perfusion of Tissues

- Shock from any cause.
- Left ventricular failure.
- Cardiac arrhythmias causing hemodynamic instability.
- Cardiac arrest.

A fall in systolic blood pressure to less than 100 mm Hg, a low cardiac output with metabolic acidosis (bicarbonate less than 18 mmoL/L), severe shock from any cause are indications for oxygen therapy.

A marked fall in the partial pressure of oxygen in venous blood (PvO_2) due to a fall in the cardiac output leads to a significant fall in the PaO_2. Also, many of these conditions

produce an increase in the physiological dead space and/or a ventilation-perfusion mismatch. It is important to maximize both the PaO_2 (and the oxygen content), as also increase oxygen transport through an increase in the cardiac output in these patients.

Acute left ventricular failure, tachyrhythms or bradyrhythms causing hemodymamic instability, and cardiac arrest are important indications for the administration of oxygen.

Poor Uptake or Utilization of Oxygen in Tissues

Poor uptake and/or utilization of oxygen in tissues is seen in septic shock, ARDS; here again the PaO_2, oxygen content and oxygen transport or delivery to the tissue cells must be adequate if cellular and organ functions are to be well maintained.

Oxygen is not utilized by tissues in cyanide poisoning as cyanide inactivates the enzyme cytochrome oxidase within the cells. A high FiO_2 is only of marginal help; reversal of cyanide toxicity by suitable antidotes is of prime importance.

Postoperative States

General anesthesia usually induces a decrease in the functional residual capacity, an increase in venous admixture and a slight to moderate ventilation-perfusion mismatch. This is particularly observed following thoracic surgery, coronary artery bypass graft surgery, open heart surgery, upper abdominal surgery and any protracted surgical procedure. A mild to moderate hypoxemia results, easily relieved by administering oxygen for an appropriate period of time.

It is important to remember that even though oxygen helps in the relief of hypoxia, it does not eradicate the root cause of hypoxia. It is therefore no substitute for adequate alveolar ventilation, neither does it solve the problem of V/Q abnormalities, nor does it abolish a right to left shunt within the lungs. Again, the oxygen content of blood is not only dependent on the PaO_2 but also on the hemoglobin concentration of the blood. The importance of an adequate cardiac output to ensure good oxygen transport cannot be overstressed. Finally, the proper uptake and utilization of oxygen by the tissue or cells is necessary if tissue hypoxia is to be countered or prevented.

Important Considerations in Oxygen Administration

When uncontrolled oxygen (at high flow rates) is given to relieve hypoxia in patients with severe COPD or in patients who suffer an acute exacerbation of COPD, relief of hypoxemia may be accompanied by a sharp rise in the arterial carbon dioxide tension ($PaCO_2$). Marked hypercapnia is undesirable and can cause a sharp fall in the pH of the arterial blood increasing both morbidity and mortality in these patients. The hypercapnia that results in the above circumstances is largely related to alveolar hypoventilation rather than to the inability of the respiratory center to respond to an increasing $PaCO_2$. This has been dealt with in the Chapter Acute Exacerbation of Chronic Obstructive Pulmonary Disease.

Therefore an important consideration is to use controlled oxygen therapy to relieve hypoxemia in patients with an acute exacerbation of COPD. This is achieved by administering oxygen through a Venturi mask (24.5% or 28%) or using low-flow oxygen at 2 L/minute via nasal prongs. Arterial blood gas analysis should be done before starting oxygen therapy. The incidence of sharply increasing hypercapnia with controlled oxygen therapy is observed only in a small percentage (13% in a recent study) of patients. If the PaO_2 during controlled oxygen therapy rises close to 60 mm Hg and the arterial pH is not lower than 7.25, controlled oxygen therapy should be continued. If however even with controlled oxygen therapy the $PaCO_2$ continues to rise so that the arterial pH falls below 7.25, or it is impossible to relieve hypoxemia (PaO_2 <55 mm Hg) without increasing hypercapnia and a falling arterial pH, other measures such as ventilator support become necessary. The ventilator support may be noninvasive or invasive depending upon prevailing circumstances (see Chapter Acute Exacerbation of Chronic Obstructive Pulmonary Disease).

One other consideration to be remembered is that in patients who hypoventilate due to neurogenic diseases, respiratory muscle weakness, poisonings (and in other conditions where to start with the lungs are essentially normal), administering oxygen will relieve hypoxemia but will have no effects on the hypercapnia observed in these patients. Finally, it should be remembered that oxygen is a dry gas and should always be humidified before administration, particularly so when the upper airway is bypassed by the use of an endotracheal tube or a tracheostomy. Ventilation of the lungs with dry gases produces heat loss, and moisture loss from the respiratory passages, and also alters pulmonary function. Heat loss causes a fall in body temperature and increases oxygen consumption. Moisture loss leads to drying or dehydration of the respiratory mucosa. The most important effect consequent to this drying is a reduced activity of the mucociliary escalator with sputum retention. Blocked airways from inspissated respiratory secretions result in ventilation-perfusion inequalities, and may lead to or accentuate hypoxia. Thus the importance of humidifying oxygen in inspired gas cannot be overemphasized.

METHODS OF OXYGEN ADMINISTRATION[4]

Routine Oxygen Therapy Using Low-Flow Oxygen

Administration Devices

A moderate rise of oxygen concentration in the alveoli suffices to relieve moderate hypoxia. An oxygen concentration of approximately 40% may be achieved by using nasal catheters, nasal prongs, or simple orofacial masks, if the flow rate is maintained between 6 L/minute and 8 L/minute. Patients cannot ordinarily tolerate flow rates higher than 6–8 L/minute through the above mentioned devices.

Nasal catheters and nasal prongs These are the simplest and most commonly used techniques of oxygen administration.

Fig. 1: Nasal prongs

Fig. 2: Simple face mask

If a nasal catheter is used, its tip should be advanced to the fold of the soft palate, and then pulled back very slightly. If it is introduced too far, it can produce gaseous distension of the stomach, as oxygen finds its way into the stomach rather than into the lungs. Irritation of the nasal mucosa can be minimized by lubricating the catheter with xylocaine jelly. The catheter can be changed from one nostril to the other every 6–8 hours.

Most units prefer nasal prongs to nasal catheters. Nasal prongs (two short plastic prongs that fit into the external nares) (Fig. 1) offer the advantage of simplicity and comfort. An added advantage over an orofacial mask is that the administered oxygen does not have to be discontinued during eating, speaking or coughing.

When oxygen is administered through nasal prongs or a nasal catheter, at a flow rate of 1–2 L/minute, the oxygen concentration is approximately 24%. At flow rates of 6–8 L/minute, the oxygen concentration approximates 40%. Further increase in flow rates are poorly tolerated and produce very little additional increase in oxygen concentration.

The effect of a given flow of oxygen through a nasal catheter or prongs is dependent not only on the flow rate, but the tidal volume and minute ventilation of the patient. If the tidal volume and minute ventilation decrease, i.e. the patient hypoventilates, then the inspired oxygen concentration will rise. Precise regulation or control over inspired oxygen concentration is thus not possible with nasal prongs or catheter. Recently developed methods of administering supplemental oxygen include the use of *reservoir cannulae, transtracheal oxygen delivery and pulsed oxygen delivery*. Transtracheal oxygen delivery is affected via a small catheter inserted into the trachea at the base of the neck. It is totally unnecessary for intensive care unit (ICU) use though it has some benefits for patients on domiciliary oxygen therapy. Pulsed oxygen devices deliver oxygen only during inspiration. This conserves oxygen, yet provides a PaO_2 equivalent to that obtained with a continuous flow system through prongs or a face mask. Pulse type devices deliver fixed oxygen volume and flow each time a pulse is triggered. Demand devices vary the volume of oxygen delivered from breath to breath depending on the depth of inspiration.

Face mask A simple oronasal plastic mask (Fig. 2) fed with oxygen at a flow rate of 6–10 L/minute, is a frequently used method for administering oxygen. The oxygen fed directly into the mask (after humidification), displaces air and creates a small oxygen reservoir. During inspiration, oxygen in the mask is inhaled; room air is also entrained through the ports and through the space between the face and the mask. The oxygen concentration of inspired gas is thus much less than 100%. The extent to which inspired oxygen concentration can increase depends on the size of the mask (and therefore of the oxygen reservoir), and the flow rate of oxygen. Higher flow rates are generally better tolerated through the use of a mask as compared to nasal prongs or catheters. At a flow rate of 6–10 L/minute, an oxygen concentration of approximately 35–55% can be achieved. The face mask is less easy and less comfortable to wear than nasal prongs. The major disadvantage is that it has to be removed when the patient speaks, eats, drinks, coughs, or expectorates.

Face mask with reservoir bag The addition of a reservoir bag to the face mask (Fig. 3) increases the potential reservoir of oxygen, and allows a further increase in the concentration of inspired oxygen. Inspired oxygen consists of oxygen from the reservoir bag of the face mask, together with some air entrained through the side ports and the small space

Fig. 3: Face mask with reservoir bag

between the mask and the skin of the face. During expiration, most of the exhaled gas passes out through the side ports, but some expired gas may return to the reservoir bag. This could lead to a fall in the partial pressure of oxygen (PO_2) and a rise in the partial pressure of carbon dioxide (PCO_2) in the reservoir bag, and should be avoided by a sufficiently high rate of oxygen flow to keep the bag washed out. Oxygen flow rates of 8–12 L/minute are commonly used with this device, and can provide an inspired oxygen concentration between 50% and 80%. The flow rate of oxygen must be so adjusted that the reservoir bag is not emptied by more than half during inspiration.

Face mask with reservoir bag and directional valves The entrainment of room air during inspiration can be almost completely prevented by covering the side ports with directional valves (Fig. 4). Except for some air passing between the mask and the face, the entire volume of inspired gas consists of oxygen from the reservoir bag and the face mask. During exhalation, the side port directional valves open and air passes out from the mask into the atmosphere. The passage of expired air back into the reservoir bag can be prevented by a directional valve.

It is important that the flow rate of oxygen fed into the mask and reservoir bag with directional valves is in the range of 10–15 L/minute. The inspired oxygen concentrations can thereby be raised in such instances to as high as 90–95%. It is also extremely important to ensure that there is no failure in oxygen supply nor a sharp fall in the flow rate, as breathing is dependent on oxygen fed into the mask-reservoir device. If the reservoir bag is inadvertently empty, asphyxia results. Table 1 compares the oxygen flow (L/minute) and oxygen concentrations (%) obtained by using low-flow oxygen administration devices.

Fig. 4: A patient breathing through a face mask with reservoir bag and directional valves

Table 1: Correlation between oxygen flow (L/min) and oxygen concentrations using low-flow oxygen administration devices

Device	*Approximate O_2 flow (L/min)*	*Approximate O_2 concentration (%)*
Nasal cannula	6	40–50
Facial mask	8	35–55
Mask with reservoir	10	50–80
Mask with reservoir plus directional valves	12	90–95

Controlled Oxygen Therapy

Principles

The purpose of controlled oxygen therapy is to relieve dangerous hypoxia by producing an adequate increase in the P_AO_2 and the PaO_2, and yet control and limit the associated rise of $PaCO_2$. This would also limit the fall in arterial pH due to respiratory acidosis.

Technique

The concentration of inspired oxygen is controlled by using high air flows with known oxygen enrichment. The principle underlying this technique is entrainment of air with constant pressure jet mixing. High air flows allow the immediate space or environment around the patient's face to be so thoroughly flushed, that there is no rebreathing and no contamination with room air. In this manner, the concentration of inspired oxygen can be controlled to within 2%.

Ventimask

The ventimask works on the Venturi principle and allows perfectly controlled oxygen administration. Oxygen is delivered to the mask through a nozzle, and the aperture of the nozzle is of set size so that as the oxygen is released through the aperture, it entrains a fixed portion of air through the side holes of the mask. Thus, if an oxygen concentration of 24% is desired, the aperture of the delivery nozzle is such that 1 L of oxygen/minute will entrain 20 L of air, and 2 L of oxygen/minute will entrain 40 L of air. The entrainment ratio is 1:20, and is independent of the flow rate; the oxygen concentration of the inspired gas is thus independent of the flow rate.

Different ventimasks have different aperture size nozzles, and provide different but fixed oxygen concentrations. For example, a mask that is designed to provide an oxygen concentration of 28% will have a nozzle aperture that allows 1 L of oxygen delivered through the nozzle to entrain 10 L of air through the side holes, i.e. a 1:10 entrainment ratio, which is again independent of the flow rate of oxygen.

As mentioned at the outset, the ventimask works on the Venturi principle, and the Venturi is fairly accurate at the recommended total flow of 40 L/minute (i.e. 2 L of oxygen/minute for a 24% mask, and 4 L of oxygen/minute for a 28% mask). The gas flow around the patient's nose and mouth flushes the mask continuously, washing out the expired carbon dioxide, and ensuring that the patient only breathes the oxygen-air mixture provided to him.

The greatest advantage of the ventimask is that the oxygen concentration it provides is independent of the flow rate, and also independent of the patient's tidal volume and minute ventilation. It can be easily used by all nurses, and requires no special adjustment. Also, the concentration of oxygen delivered is not at the mercy of faulty flow meters or reducing valves. The disadvantage as with all oronasal masks is that it has to be removed during coughing, eating, speaking, or drinking. In a seriously ill patient, removing the mask during feeds can cause a dangerous deterioration due to a sharp fall in the PaO_2 and worsening hypoxia. In severely hypoxic patients, the administration of oxygen should be continued, even when the patient is being fed, via nasal prongs at a flow rate of 1–2 L/minute; this prevents the temporary but dangerous hypoxia.

Currently, other commercially available high airflow systems have been designed to deliver oxygen concentrations varying from 24% to 50%, using the same principle as the Venturi mask. A jet of oxygen from a wall or tank source is passed through a precisely designed (exact size) orifice, and this results in the entrainment of room air through the ports in the surrounding cylinder.

Nasal Prongs

Many ICUs in Mumbai and other large cities (leave aside smaller towns all over the country), do not use ventimasks or other high airflow oxygen-enriched delivery systems to provide controlled oxygen therapy. It is recommended that in the absence of these devices, nasal catheters or nasal prongs be used in an attempt to give controlled oxygen therapy. Oxygen at a flow rate of 1–2 L/minute through nasal prongs or catheters is generally effective in providing controlled oxygen concentrations of 24–28% in inspired gas. The flow rate should be initially kept at 1 L/minute; if this is well tolerated, it is increased to 2 L/minute. Measurements of the PaO_2 and the $PaCO_2$ are of help, and the patient is kept under a close watch, especially as regards his ventilation. If the patient has marked hypoventilation, administration of oxygen even at 1–2 L/minute can lead to an uncontrolled or higher than desired concentration of oxygen. In such patients, the flow rate should be reduced to less than 1 L/minute. Oxygen delivered through nasal prongs or catheters at low flow rates as stated above, is generally effective in relieving hypoxia without producing a dangerous rise in the PCO_2.

Hyperbaric Oxygen

Hyperbaric oxygen is not administered in the ICU. Yet some critically ill patients under intensive care have to be transported to hyperbaric oxygen chambers in the same or distant hospitals to avail of this therapy. The administration of oxygen at higher than atmospheric pressure has certain advantages. When breathing air at atmospheric pressure, the oxygen in solution in plasma is 0.3 mL/dL; when breathing oxygen at a pressure of 2 atm, it is 4.5 mL/dL. This is just a little less than the amount of oxygen taken up by tissues in unit time, and goes a long way in aiding jeopardized tissue perfusion, and relieving tissue hypoxia. The main use of hyperbaric oxygen is in the treatment of carbon monoxide poisoning. The dissolved oxygen relieves hypoxia, and the markedly increased oxygen tension helps the quick dissociation of carbon monoxide from COHb. Hyperbaric oxygen therapy is also useful in the management of sepsis secondary to wounds contaminated by anaerobic gas-forming organisms, and in the treatment of wounds with a poor blood supply. Hyperbaric oxygen is also used in the treatment of an ischemic limb where definitive surgical or non-surgical techniques are either not indicated or have failed.

Humidification of Oxygen and Inspired Gas[5]

Oxygen is dry and should always be humidified before administration. Ventilation of the lungs with dry gases produces heat loss, and moisture loss from the respiratory passages, and also alters pulmonary function. Heat loss causes a fall in body temperature and increases oxygen consumption. Moisture loss leads to drying or dehydration of the respiratory mucosa. The most important effect consequent to this drying is a reduced activity of the mucociliary escalator with sputum retention. Blocked airways from inspissated respiratory secretions result in ventilation-perfusion inequalities, and may lead to or accentuate hypoxia. Thus, the importance of humidifying oxygen in inspired gas cannot be overemphasized.

When oxygen is administered by nasal prongs, nasal catheters, or a facial mask, the upper respiratory passages, particularly the nose, will normally humidify the inspired gas. Even so, oxygen should preferably be humidified before administration. When upper respiratory passages are bypassed by an endotracheal or tracheostomy tube, humidification becomes absolutely mandatory.

It should be noted that even if room air or administered oxygen is saturated to 100% with water vapor at room temperature, this saturation drops considerably when it comes into contact with respiratory passages whose normal temperature is 37°C. The fall in saturation is even greater if the body temperature is higher, as in patients running fever. Therefore to prevent drying of the respiratory mucosa either the air or oxygen inspired by the patient should be saturated

Fig. 5: A bubble humidifier

Fig. 6: A heated vaporizer

with water vapor at 37°C; or the inspired air or oxygen should be supersaturated by suspending water droplets in it at room temperature. When this supersaturated oxygen or air is warmed during its passage through the trachea, the suspended droplets vaporize and provide a humidity of well-nigh 100%.

There are a number of techniques for humidification. All modern ventilators are provided with humidifiers with temperature control of the humidified gas delivered to the patient, as also with nebulizers, which allow nebulization of inspired gas or nebulization of drugs into the respiratory tract.

Devices for the humidification of inspired gas or oxygen can be broadly divided into those that add water to gases, and those that retain water from expired gases (heat and moisture exchangers).[6]

Devices Adding Water to Gases

Vaporizers (unheated)[7]. A bubble humidifier is an example of an unheated vaporizer (Fig. 5). When oxygen is moistened by bubbling it through a large surface of water, because of the heat loss by vaporization, the temperature of oxygen falls below the ambient temperature, at flow rates greater than 6 L/minute. The cooled gas has sufficient moisture, but when it comes into contact with the warm respiratory mucosa, the water vapor saturation falls to 20–25%. With nasal prongs or a face mask, this method suffices as warmth and humidification are supplied by the nose, mouth and pharynx. A bubble humidifier is however quite inadequate for humidification of oxygen or inspired gas in patients with an endotracheal tube or tracheostomy.

Heated vaporizers (Fig. 6)[8-10] The Blower Humidifier devised by Spalding,[11] is a good example of this type. Air or oxygen from a blower or a mechanical ventilator is passed over a surface of water thermostatically maintained at a temperature of 45–55°C. The inspired gas is 100% saturated at this temperature, and the thermostat is set so that the air or oxygen is delivered to the patient at about 37°C. At this temperature, the inspired gas or oxygen is saturated to about 70–90%. The blower humidifier tends to get overheated, and the temperature of inspired gas should therefore be frequently checked to prevent thermal injury to the respiratory passages. There is also a risk of bacterial colonization of the water in the reservoir, or in the delivery tubing.

Fig. 7: Ultrasonic nebulizer

Nebulizers Various nebulizers can be used to suspend water particles in inspired gas. The water droplets should be 1–10 µm in diameter. Larger droplets are of no use as they get deposited within the delivery tubes. Smaller droplets are stable and are not deposited in the respiratory tract. Nebulizers can be gas driven (Fig. 7) mechanically actuated (e.g. spin disc nebulizer), or ultrasonic.[12]

The main disadvantage of gas driven and mechanically actuated nebulizers is the risk of microbiological contamination of the reservoir. This can be dangerous as microbes suspended in the aerosol can reach deep into the lungs, right up to the alveoli. Ultrasonic nebulizers are costly and can cause overhydration, as most devices can produce water well in excess of 250 g/m^3, and some, over 1000 g/m^3.[12] Bacterial contamination of the aerosol can also occur.

A saline drip through the tracheostomy tube In a patient with a tracheostomy, when the above described methods are not available because of financial or other constraints, an easy and effective method of humidification of inspired gas, is to drip normal saline slowly into the tracheostomy tube through a thin sterile plastic catheter, at the rate of 10–12 drops/minute or 16 mL/hour. With a minute ventilation of 8 L/minute, this gives a theoretical humidity of 31 mg/L to the inspired gas.[13]

Devices Retaining Water from Expired Gases

Heat and moisture exchangers (HME)[7,14] An HME is a device which when connected to an artificial airway will extract heat and moisture from the expired gas, and will return this heat and moisture to the inspired gas during inspiration. Ideally an HME should retain at least 70% of expired moisture. HME devices include Condenser Humidifiers, Hygroscopic Condenser Humidifiers and Hydrophobic Condenser Humidifiers. Filtration of inspired and expired gases can be provided by the associated use of heat and moisture exchanging filters.

HME devices have important advantages—

- Humidification is satisfactory with artificial airways (endotracheal or tracheostomy tubes).
- The breathing circuit remains dry.
- They are comparatively inexpensive, disposable, and do not require an external power source.

They cannot however provide very high levels of humidification, and ventilation can be obstructed if sputum is expectorated on the exchanger membrane. Some HME devices have a significant internal volume, and therefore increase the dead space. This is a disadvantage in a spontaneously breathing patient with a reduced tidal volume. These devices also produce a slight increase in the resistance to breathing, and when saturated with water vapor, result in a significant obstruction to airflow.

In conclusion, humidification of inspired gases is necessary for all critically ill patients receiving ventilatory support, for those breathing through a tracheostomy or endotracheal tube, and for those who have been breathing spontaneously, but have recently been extubated. The humidifier used should produce adequate saturation of the inspired gas or oxygen with water vapor. Heat and moisture exchangers have greater advantages as compared to hot water bath humidifiers. Bacterial colonization is a major risk and can result in nosocomial pneumonia. The use of filters that prevent bacterial or viral contamination of humidified inspired gas helps to decrease the incidence of this complication.

COMPLICATIONS OF OXYGEN THERAPY

Progressive Hypercapnia[15]

The danger of progressive hypercapnia, particularly after uncontrolled oxygen therapy in a number of patients with hypoxia due to COPD, has already been discussed (also see Chapter Acute Exacerbation of Chronic Obstructive Pulmonary Disease).

Circulatory Depression

This is very rare, but has been occasionally observed in patients who have been acutely, severely hypoxic, and whose circulation is maintained by excessive sympathetic activity and excessive catecholamine discharge, induced by the severe hypoxia. Sudden relief of hypoxia abolishes this sympathetic overactivity, causing temporary hypotension, and occasionally circulatory collapse. We have observed this phenomenon following sudden relief of acute severe hypoxia in glottic or subglottic obstruction, after establishing an open airway (through a tracheotomy) and administering a high concentration of oxygen. Circulatory depression is temporary, and can be corrected by a volume load, or by an infusion containing a sympathomimetic agent.

Drying and Crusting of Secretions in the Respiratory Tract

Oxygen should always be humidified prior to administration. This is particularly imperative in patients with artificial airways. Unhumidified oxygen causes drying of secretions, and this can result in blockage of the bronchi by inspissated mucus. Partial or complete blockage of artificial airways (endotracheal or tracheostomy tube) by crusted secretions can have disastrous consequences.

Danger of Oxygen Withdrawal

Moderate or severe hypoxia warrants continuous oxygen therapy till such time as the hypoxia is relieved. Some hypoxic COPD patients may become drowsy or disoriented even on controlled oxygen therapy. To discontinue oxygen in such a situation is dangerous and wrong. If oxygen administration is stopped with the $PaCO_2$ markedly elevated, the P_AO_2 (and consequently the PaO_2) falls to an even lower level than that prior to starting oxygen therapy. This is because the P_ACO_2 has risen to a higher level than that prevailing at the start of oxygen therapy. Such patients therefore have a worsening of their already severe hypoxic state. Intermittent oxygen therapy can be dangerous in a hypoxic patient, and is wrong on principle. It only serves to give periods of relief from hypoxia, followed by periods of worsening and often extreme hypoxia. Oxygen, if indicated, needs to be given continuously till hypoxia is relieved.

Oxygen Toxicity

Lung Toxicity

High concentrations of oxygen over a prolonged period of time can produce changes in the lungs characterized by atelectasis, damage to the surfactant, interalveolar edema, and interstitial thickening and fibrosis. It is generally accepted that oxygen concentrations up to 50% are safe for long periods. We have used 60% oxygen for weeks, and have observed that the patients have recovered without residual effects. We have also been forced to use 100% oxygen in two patients (who would otherwise have died of hypoxia) for as long as 24 hours, followed by 80–90% oxygen for the next 4–7 days, and then 60–70% oxygen for another week. Both patients survived without any significant residual damage to the lungs. This does not mean that very high oxygen concentrations should be used with abandon. It does however signify that in our experience, the use of 100% oxygen is not as lethal as is often made out to be.

The practical applications to be derived from experimental and clinical studies on oxygen toxicity are summarized below—

- For patients with chronic hypoxemia (as in severe chronic airways obstruction), it is sufficient to use a concentration of oxygen that will correct dangerously low PaO_2 levels. A PaO_2 between 55 mm Hg and 60 mm Hg (O_2 saturation—90%) is generally adequate in these patients.
- Positive end-expiratory pressure (PEEP) should be used during mechanical ventilation if an inspired oxygen concentration greater than 50% fails to relieve dangerous hypoxia in patients with acute pulmonary disease.

In acute pulmonary problems with severe hypoxia, the oxygen concentration must be sufficient to allow an oxygen saturation of about 90%. If in spite of the use of PEEP, very high oxygen concentration (>80%) is needed over a prolonged period of time to maintain an oxygen saturation of 90%, it may be permissible to allow mild to moderate hypoxemia (O_2 saturation around 85%) so as to enable a reduction in the FiO_2. The degree of hypoxia one allows will depend on the patient's tolerance to hypoxia, the age of the patient, and the ability or otherwise to increase oxygen transport to the tissues.

Life-threatening hypoxia must always be relieved, even if this requires the use of 100% oxygen for prolonged periods of time. The fear and danger of possible oxygen toxicity is never an argument to allow a patient to irreversibly deteriorate and die of hypoxia.

It is difficult, if not impossible, to detect signs of lung toxicity due to high oxygen concentrations in critically ill individuals with serious pulmonary problems. A fall in the compliance and the PaO_2 can occur due to very high oxygen concentrations, but it may be impossible to ascertain in clinical practice, whether this is related to the disease, or is iatrogenic due to oxygen toxicity.

Retrolental Fibroplasia

This complication occurs in the neonatal period, and is related to high PaO_2 levels. If the inspired oxygen concentration is high enough to raise the PaO_2 to about 160 mm Hg even for a few hours, retrolental fibroplasia can occur. Therefore in neonates, PaO_2 levels should never equal or exceed 100 mm Hg.

Cerebral Oxygen Toxicity

This is occasionally observed when oxygen is breathed at hyperbaric pressures above one atmosphere. The syndrome is chiefly characterized by epileptic fits and is termed the Paul Bert effect, after the individual who first described it.

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CHAPTER 30

Airway Management

ESTABLISHING THE AIRWAY

Nothing is more critical in emergency respiratory care than ensuring a patent airway and then maintaining it. An obstructed airway can lead to death within a few minutes. In patients with cardiac arrest, inability to secure a patent airway generally renders all efforts at cardiopulmonary resuscitation ineffective.

UPPER AIRWAYS OBSTRUCTION

Upper airways obstruction may result from soft tissue obstruction or from laryngeal obstruction. Soft tissue obstruction is probably the most common airway emergency. It results from the encroachment on the patency of the upper airway by soft tissues of the pharynx or by tissue in close relation to the pharynx. Upper airways obstruction is thus seen in comatose patients when the pharynx loses its tone or in patients with lower cranial nerve palsies when the pharynx is paralyzed. It also occurs in angioneurotic edema, inflammation, retropharyngeal abscess, and can be caused by bleeding and soft tissue tumors within that area. Foreign bodies, dentures, vomitus, blood clots, thick oropharyngeal secretions can also block the upper airway. The common factor underlying all these causes of upper airways obstruction is the absent or the markedly diminished patency between the base of the tongue and the pharyngeal wall. Obstruction at the larynx can be caused by laryngeal spasm as in tetanus, by a bilateral vocal cord abductor palsy, by inflammatory or neoplastic lesions above or within the larynx or by laryngeal edema. A foreign body or food (such as a piece of meat) may also obstruct the larynx and cause severe asphyxia and death. Partial upper airways obstruction is characterized by noisy breathing, akin to snoring. Partial upper airways obstruction can be easily missed, particularly in comatose patients who in addition often hypoventilate due to a depressed respiratory center. Laryngeal or tracheal obstruction gives rise to a high-pitched inspiratory sound termed stridor. Complete or almost complete airways obstruction results in marked inspiratory efforts with little or no movement of air into the lungs. There is severe retraction of the intercostal spaces, the sternum and epigastrium, together with strong contraction of the accessory muscles of respiration during inspiratory efforts. The patient, to start with, is extremely distressed, restless and anxious; and becomes increasingly cyanosed. Tachycardia or a bradyarrhythmia is related to hypoxia. Death ensues if hypoxia is unrelieved.

MANAGEMENT

The treatment obviously is to relieve soft tissue obstruction by simple basic maneuvers.

Neck Extension with Forward and Upward Chin Thrust

This should be the first maneuver to be attempted as it can promptly relieve mild to moderate obstruction by increasing the patency between the back of the tongue and the pharynx. Careful suction of secretions, blood and vomitus from the pharynx may be necessary, as also the removal of dentures or a foreign body that may be obstructing the airway.

Bag-Mask Ventilation

Once the above basic maneuvers have been accomplished, it is important to ventilate the patient so as to prevent and combat hypoxia. The immediate and simplest way to attempt this is through Bag-mask ventilation. Next only to cardiac compressions, bag-mask ventilation is of crucial importance

in a patient with cardiac or cardiopulmonary arrest. It is also the initial step in a patient with a semi-obstructed airway or in a patient acutely hypoxic from any cause. Bag-mask ventilation is often preparatory to the possible need to intubate the patient so as to secure the airway. As far as possible, endotracheal intubation should be performed by an individual with the requisite experience and expertise. Attempts to abandon bag-mask ventilation and intubate the patient by inexperienced personnel have often proved harmful. Unsuccessful attempts to intubate with damage to the airway make a subsequent attempt at intubation by even an experienced individual difficult.

Technique

The mask should cover the bridge of the patient's nose at the upper end and should cover the mouth at the lower end; so that the nose and mouth are enclosed by the mask. The doctor stands at the patient's head, presses the mask down with the left hand. The thumb fixes the nasal portion of the mask and the index finger is over the oral portion, the rest of the fingers of the left hand are spread over the left side of the patient's mandible so as to push it forward. The bag attached to the mask is alternatively squeezed and relaxed with the operator's right hand at 15–18 times per minute so that air (or 100% oxygen if the bag is connected to an oxygen supply) is pushed via the mask into the airway and into the lungs with each squeeze of the bag. The success of bag-mask ventilation is judged by the rhythmic rise and fall of the patient's chest with each squeeze and relaxation of the bag, by satisfactory auscultatory breath sounds and generally by improvement of the patient's oxygen saturation. The lung chest compliance can be roughly assessed by the amount of pressure or force required to squeeze the bag. The minimum pressure or squeeze should be used to satisfactorily expand the chest so as to decrease the risk of insufflating the stomach with gas as this could increase the risk of aspiration.

Management of Aspiration during Bag-Mask Ventilation

Danger of aspiration is significant in high-risk patients—those with a full stomach, patients with a hiatus hernia or gastroesophageal reflux, obese individuals and in pregnancy. Aspiration should be countered by maintaining pressure over the cricoid cartilage (thereby closing the esophageal lumen), putting the patient promptly in the Trendelenburg position and suctioning the gastric contents. If possible, intubation should be performed with the help of direct laryngoscopy. The airway should be secured and the cuff of the endotracheal tube inflated before resuming positive-pressure ventilation.

Airway Adjuncts

If positioning of the head and neck with clearing of secretions (or foreign material) from the mouth fails to establish a clear airway, several airway adjuncts are available if an individual with necessary expertise for intubating the patients is not available. The oropharyngeal and nasopharyngeal airways are simple airway adjuncts that can be of use to keep the upper airway patent if head positioning has not sufficed. These are briefly described below.

Oropharyngeal Airway

This device is a conduit inserted along the top of the tongue until the teeth or gums limit its insertion. It is positioned between the base of the tongue and the pharynx (separating the two) thereby maintaining a patent airway. The airway should be inserted with its curve up initially and rotated into position when the end reaches the base of the tongue. It is designed to permit a suction catheter to pass through it, and allow suction of secretions in the pharynx and upper larynx. An oropharyngeal airway is chiefly suited for comatose patients and that too for limited periods of time. As it rests at the base of the tongue, it stimulates the gag reflex, and can induce excessive salivation, vomiting and even laryngospasm in the conscious patient.

Nasopharyngeal Airway

The nasopharyngeal airway is a pliable plastic tube inserted (after lubrication) through the nares to follow the posterior wall curvature of the nasopharynx and oropharynx so that its tip rests on the base of the tongue, separating it from the pharyngeal wall. This airway is better tolerated than the oropharyngeal airway by the semiconscious and fully awake patient. It can prevent or relieve soft tissue upper airways obstruction and allows suctioning of the pharynx through a suction catheter passed through the airway. The nasopharyngeal airway can cause bleeding and airway trauma through pressure necrosis. Some advocate daily changing of the airway from one nare to the other to minimize trauma to the nasal passages. We very rarely use the nasopharyngeal airway in our unit (Fig. 1).

ARTIFICIAL AIRWAYS

An artificial airway is a conduit or tube inserted into the trachea bypassing the pharynx and larynx, which no longer form part of the total airway. In essence, this means endotracheal intubation or tracheostomy.

Indications

1. Hypoxia and/or hypercapnia (due to acute respiratory failure) severe enough to necessitate invasive ventilator support through an endotracheal tube or a tracheostomy is the prime indication for the insertion of an artificial airway. In certain circumstances, noninvasive ventilator support is preferred to invasive ventilator support at least to start with. When noninvasive ventilator support fails or is contraindicated, invasive ventilator support is mandatory. Noninvasive ventilator support, its indications and contraindications have been discussed later in another chapter.

Fig. 1: Maintaining a clear airway by triple airway maneuver: (1) Tilt head backward; (2) Lift mandible forward and (3) Open the mouth and try to remove any foreign body

2. To maintain an open airway in the presence of obstruction to the pharynx or larynx. Obstruction to the upper airway could be caused by trauma to the mandible or larynx, or the inhalation of smoke or noxious chemicals. Obstruction could also result from acute epiglottitis (particularly in children), a large retropharyngeal abscess or hematoma or a subglottic stricture. Laryngeal edema and/or laryngeal spasm are important causes of upper airway obstruction. Finally, tumors involving the upper airway may lead to obstruction necessitating endotracheal intubation. If the obstruction is such that it is technically impossible to do an endotracheal intubation one has no option other than to perform a tracheostomy.
3. To protect the airway in a patient whose protective reflexes are poor. The pharynx, vocal cords and the epiglottis play an important role in protecting the airway from aspiration of secretions, foreign matter, food or regurgitating gastric contents. The reflexes that normally protect the airways are: (1) the pharyngeal reflex, which normally includes the gag and swallowing reflexes; (2) the laryngeal reflex, which is a vagal reflex, and is responsible for the apposition of the vocal cords, and closure of the epiglottis on stimulation of the larynx by secretions or by foreign matter; (3) the tracheal reflex, which is a vagal reflex causing cough when the trachea is stimulated by some irritant or foreign matter and (4) the carinal reflex, which is a vagal reflex causing cough and irritation of the carina. The protective reflexes are generally obtunded from above downward, irrespective of whether the cause of obtundation is due to drugs, disease or a deepening state of unconsciousness. When these reflexes return in a recovering patient, they recover from "below-up". The preservation of the pharyngeal reflex (gag reflex) therefore suggests preservation of the laryngeal and tracheal reflexes. However, the gag reflex is believed to be diminished or inelicitable in 10% of the normal population. Therefore, absence of this reflex does not always indicate absence of other protective reflexes. Clinically, the inability to handle secretions in the upper airway and to swallow in a coordinated manner denotes a loss of protective airway reflexes and necessitates the establishment of an artificial airway. In such patients, the artificial airway also seals the respiratory from the alimentary tract, thereby preventing aspiration of gastric contents into the tracheobronchial tree (Box 1).
4. To facilitate suction of secretions (from within the tracheobronchial tree), which the patient is incapable of coughing up and expectorating. This could be because the secretions are copious, the cough reflex is poor, or the patient is just too feeble to cough and expectorate. Although it is possible to insert a suction catheter through the vocal cords for suctioning tracheal secretions, it is not advisable to do so except on rare occasions. Laryngeal edema and obstruction, and precipitation of fatal arrhythmias in critically ill patients can occur following such attempts. The establishment of an artificial airway allows easy, safe and direct suctioning of the tracheobronchial tree.

Box 1: Indications for artificial airway

- Acute respiratory failure necessitating invasive ventilator support
- To maintain an open airway in the presence of obstruction to the pharynx or larynx
- To protect the airway when protective reflexes are lost
- To facilitate suction of secretions within the tracheobronchial tree which the patient is unable to cough up and expectorate

Disadvantages of Artificial Airways

The establishment and maintenance of an artificial airway (endotracheal intubation or tracheostomy) has its hazards and complications depending on the expertise with which it is established, the quality of after care, and the nature and degree of the critical illness in the patient. These complications are dealt with later. However, there are some inherent universal drawbacks of artificial airways, which need to be considered.

1. An artificial airway bypasses the normal defence mechanisms, which counter bacterial contamination of the airways. The airways and lungs are more prone to nosocomial infection.
2. An endotracheal tube removes the effectiveness of cough because the vocal cords are nonfunctional; a tracheostomy bypasses the cords.
3. An artificial airway prevents the patient from communicating vocally. This can be frustrating and frightening, and it is important, in a conscious patient, to provide a pad and a pen to help the patient communicate in writing.

4. In a conscious patient, there is often a feeling of a loss of dignity and a loss of control over one's self due to tubes which prevent the patient from speaking or breathing normally.

ESTABLISHING AN EMERGENCY AIRWAY

An emergency airway is one that must be established immediately, with utmost urgency, as it involves a matter of life and death. The chief indications for an immediate airway are—

- Severe life-threatening upper airways obstruction.
- Cardiac or respiratory arrest—or impending cardiorespiratory arrest.
- Fulminant pulmonary edema.

The emergency airway of choice is an oral endotracheal intubation, with the aid of direct laryngoscopy. In an intensive care unit (ICU) or in any setting where the expertise and the necessary equipment is promptly available, oral endotracheal intubation can be performed in a matter of minutes. However, emergency endotracheal intubation may prove difficult even in experienced hands, and at times, may fail. In such circumstances, an alternative airway needs to be established urgently.

OTHER EMERGENCY AIRWAYS

Laryngeal Mask Airway

The laryngeal mask airway (LMA) can secure the airway in an emergency, in a situation where endotracheal intubation fails, or in a situation where experienced personnel to intubate are unavailable. A properly placed LMA not only secures the airway, but allows ventilatory support and reduces the risk of gastric aspiration. A standard adult LMA consists of a 12-mm internal diameter tube fused at a 30° angle to an elliptical spoon-shaped cuff with an inflatable rim. The cuff is soft and when inflated adapts to the shape of the larynx forming an airtight seal over it. The tube opens into the concavity of the cuff ellipse through a fenestrated aperture. The LMA should be placed with the patient placed in sniffing position—neck flexed and head extended. The cuff is deflated and lubricated prior to insertion. The patient's mouth is opened and with the distal aperture of the cuff positioned anteriorly, the tip of the cuff is applied against the hard palate and advanced by the index finger of the right hand over the back of the tongue till it meets resistance when it abuts on the upper esophageal sphincter. The cuff is inflated with 10–30 mL air, so that the cuff centers on the laryngeal inlet. Studies show that the procedure is easily learnt by nurses and that adequate ventilation could be provided in 87% of cases.[1] Studies in mannequins suggest that the LMA decreased gastric distension compared to the artificial manual breathing unit (AMBU) and could be more easily placed than the combitube (Fig. 2).[2]

Intubating Laryngeal Mask Airway

The standard LMA can allow intubation with the aid of a fiberoptic bronchoscope. However, the size of the endotracheal tube that can be inserted through the LMA is necessarily small. The intubating LMA (I-LMA) consists of an anatomically curved rigid tube with a metal-guided handle and a distal silicone laryngeal cuff. The floor of the cuff aperture has an epiglottis elevating bar and guiding ramp, which permits an especially designed endotracheal tube (8 mm in diameter) to be directed toward the glottis and inserted blindly into the trachea. The I-LMA can be placed without moving the patient's head or neck. This is of definite advantage to patients who have sustained an injury to the cervical spine or to those who have an unstable cervical spine—situations where spinal flexion is best avoided.

Fig. 2: Laryngeal mask airway

The major concerns in the use of the LMA are: (1) the risk of gastric aspiration, (2) the possibility of ineffective ventilation because of suboptimal positioning over the larynx, (3) the inability to generate high inflation pressures in patients with increased airway resistance or low lung compliance.

Cricothyroidotomy (see Chapter Procedures in the Intensive Care Unit)

A cricothyroidotomy with insertion of a tube or a conduit into the trachea may serve as a life-saving temporary emergency procedure. A cricothyroidotomy should be replaced by an appropriate airway as soon as possible.

Emergency Tracheostomy

An emergency tracheostomy can be performed by an experienced surgeon in 15 minutes.

Percutaneous Tracheostomy (see Chapter Procedures in the Intensive Care Unit)

A percutaneous tracheostomy can be carried out by an experienced intensivist or surgeon in perhaps even lesser time. Till such time as an emergency airway is ultimately secured, it is vital to continue to ventilate the patient with a bag-mask using 100% oxygen and to ensure that at least the upper airway (above the vocal cords) is patent.

Endotracheal Intubation (also see Chapter Procedures in the Intensive Care Unit)

Endotracheal intubation is often performed electively and in less emergent situations. It can be performed—

- *With the patient awake* This is very unpleasant for the patient but has the great advantage that it allows the patient to ventilate and oxygenate himself or herself. It is preferred particularly in patients with difficult airways. The approach may be a blind nasotracheal intubation or endotracheal intubation using topical anesthesia and direct laryngoscopy to visualize the larynx, or endotracheal intubation through the use of a fiberoptic bronchoscope.
- *With the patient sedated* Sedative agents such as midazolam or propofol are administered as a bolus. The patient although sedated, maintains spontaneous ventilation. Endotracheal intubation is then done with the aid of direct laryngoscopy, or if needs be with the help of a laryngoscope or a bronchoscope. If an LMA has been introduced earlier, intubation can be done via a fiberoptic bronchoscope passed through the larynx.
- *After inducing neuromuscular paralysis* This is the method most frequently used when performing endotracheal intubation with the aid of direct laryngoscopy. Muscle paralysis with relaxation of the masseters and paralysis of the pharynx generally allows a good view of the larynx with the aid of a laryngoscope and allows quick intubation. However, respiratory muscle paralysis abolishes spontaneous ventilation and the physician must therefore obtain immediate airway control, or failing this, ensure effective bag-mask ventilation till spontaneous ventilation returns. Also, in a difficult intubation, the larynx if situated anteriorly may not be visualized even after neuromuscular paralysis, so an alternative plan to secure the airway and maintain ventilation should be promptly available. A standard rapid sequence method is followed when using neuroparalytic agents prior to endotracheal intubation in patients at risk for aspiration of gastric contents.
  - The patient is oxygenated with 100% oxygen for some minutes through a bag and full-face mask.
  - A sedative (midazolam) is administered as a bolus followed immediately by the administration of the neuroparalytic agent.
  - At the same time, an assistant exerts pressure on the cricoids using the Sellick's maneuver, which occludes the esophagus and reduces the risk of aspiration.
  - Endotracheal intubation is quickly performed, the pressure on the cricoid being relieved only after the airway has been secured.

The major disadvantage of neuromuscular paralysis is that effective spontaneous respiration may not return for several minutes so that a failed intubation can turn into a disaster (Table 1).

The procedure for endotracheal intubation has been described in the Chapter Procedures in the Intensive Care Unit. The position of the head and neck for endotracheal intubation is illustrated in Figure 3. Figure 4 shows the endotracheal tube in place.

Complications of Endotracheal Intubation

Complications during Intubation

1. Damage to the lips, teeth, pharynx and larynx can occur when performed in a hurry or when performed clumsily. The vocal cords can be badly bruised and injured and a dislocation of the arytenoid cartilage could occur. A broken tooth can be aspirated and lodged within a bronchus. Perforation of the pharynx and damage to or even perforation of the trachea has been reported. Aspiration of stomach contents is to be guarded against, particularly in a patient with a full stomach.
2. The endotracheal tube instead of being positioned above the carina may be pushed into the right main bronchus. The left lung is then unaerated and becomes atelectatic.

Cardiovascular complications A number of cardiovascular complications can occur during intubation. Ventricular arrhythmias occur in 5–10% of patients. Ventricular tachycardias and rarely ventricular fibrillation may be observed. Patients with myocardial ischemia or patients with a fresh myocardial infarction are particularly susceptible to ventricular arrhythmias and even to cardiac arrest. Lignocaine prophylaxis (75 mg IV) or amiodarone prophylaxis (150 mg IV) can be used, particularly in patients with ischemic heart disease who have ventricular extrasystoles. Delay in intubating a patient with cardiac arrest may potentiate dangerous hypoxia with all its complications. Bradyrhythms during intubation have also been reported. They generally respond to IV atropine. Both hypotension and hypertension can occur during intubation and may necessitate urgent treatment.

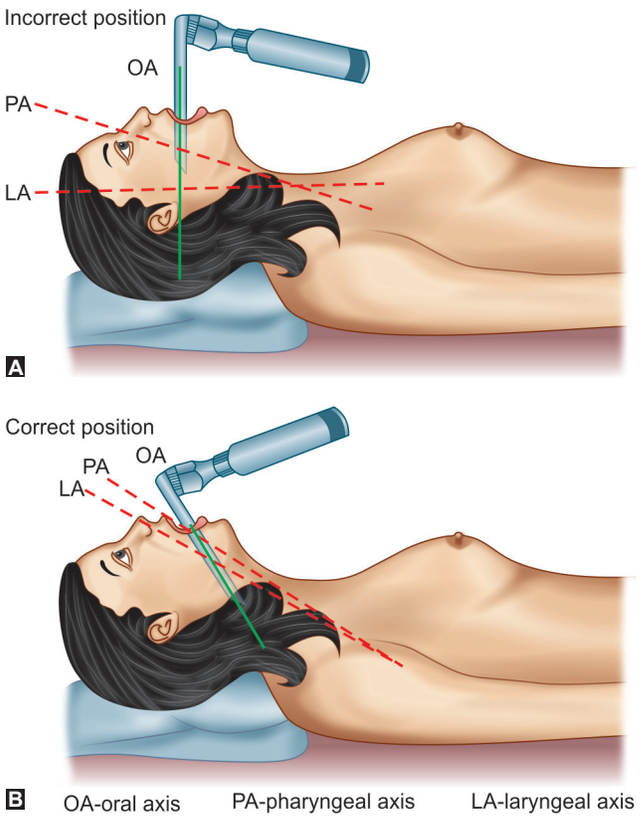
Complications When the Tube Is in Place

The greatest danger is blockage of the tube causing hypoxia and death if not promptly recognized and corrected. Kinking of the tube can also occur. The tube sometimes is inadvertently advanced or slips into a bronchus (generally the right main bronchi). The tube can erode the trachea anteriorly and can cause severe bleeding through erosion of vascular structures in the mediastinum. A sudden spurt of bleeding should suggest this diagnosis. The tube could also erode posteriorly into the esophagus causing a tracheoesophageal fistula. Both the above situations warrant an urgent bronchoscopy with a careful look at the mucosa underlying the cuff. Other complications include tracheomalacia, damage to the vocal cords and subglottic stenosis, the later being evident on extubation. A cuff leak in a patient on ventilator support can lead to hypoventilation. It can be countered by appropriately increasing the tidal volume. The tube may however need to be changed. Finally, nosocomial pulmonary infection is a dreaded complication, the most important and common being a ventilator associated pneumonia (Box 2).

Table 1: Drugs used during endotracheal intubation

Drug	*Action*	*IV (mg/kg)*	*Onset of action*	*Side-effects*
Thiopental	Induction	2.5–4.5	20–50 seconds	Hypotension
Propofol	Induction	1.0–2.5	<1 minute	Hypotension
Midazolam	Induction	0.02–2.0	30–60 seconds	Hypotension
Ketamine	Induction	0.5–2.0	30–60 seconds	Increased secretions and raised ICT
Rocuronium	Relaxant	0.6–1.0	60–90 seconds	–
Succinylcholine	Relaxant	1–2	45–60 seconds	Increased intragastric and intracranial pressure; hyperkalemia

Abbreviation: ICT, intracranial tension.



Figs 3A and B: The position of the head and neck for endotracheal intubation

Fig. 4: Endotracheal intubation, with the tube in place

Box 2: Complications of endotracheal intubation

- Complications during intubation—
  - Damage to lips, teeth, pharynx, larynx, trachea (including perforation and laceration)
  - Dislocation of arytenoid cartilage
  - Aspiration of gastric contents
  - Insertion of tube in right main bronchus
  - Hypoxia due to delayed intubation
  - Cardiovascular complications—
    - Ventricular extrasystoles
    - Ventricular tachycardia
    - Bradyrhythms
    - Hypotension, hypertension
- Complications with the tube in place—
  - Blockage of tube
  - Kinking of tube
  - Cuff leak
  - Advancement of tube into the right main bronchus
  - Displacement of tube above larynx
  - Damage to vocal cords
  - Nosocomial pulmonary infection: tracheitis, tracheobronchitis, nosocomial pneumonia
- Complications after extubation—
  - Laryngeal spasm, laryngeal edema
  - Postglottic stenosis
  - Laryngitis, laryngeal ulcerations, laryngeal granuloma
  - Vocal cord paralysis
  - Vocal cord synechiae

DIFFICULT AIRWAY

A difficult airway is a clinical situation in which an anesthesiologist or an intensivist experiences difficulty with bag mask ventilation, or difficulty with tracheal intubation or both. Difficult bag-mask ventilation implies an inability to maintain an O_2 saturation more than 90% using 100% oxygen and positive-pressure bag-mask ventilation. Difficult intubations are those requiring three or more attempts using conventional laryngoscopy. In an ICU setting, a difficult-to-intubate airway may be apparent on a preintubation evaluation or becomes manifest only on attempted intubation. A markedly receding jaw, prominent incisors, macroglossia, soft tissue lesions obstructing the oropharynx or the entrance to the larynx, a rigid spine as in ankylosing

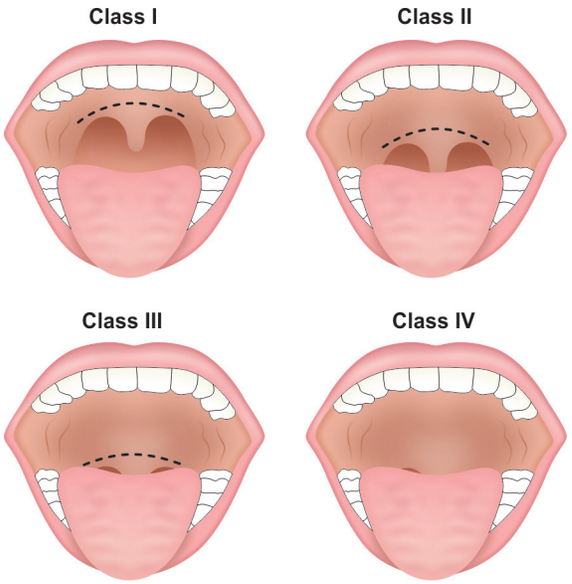


Fig. 5: Mallampati classification
Class I: Clearly visible fauces, uvula, with a wide oropharynx
Class II: Less clearly visible fauces and uvula, with a smaller opening of the oropharynx
Class III: Poorly visible fauces, uvula with a small oropharynx
Class IV (added by Samson and Young): Inability to see the fauces, uvula and the oropharyngeal opening

spondylitis or a very anteriorly placed glottis can make intubation difficult or impossible.

Mallampati assessed the ability to perform a direct laryngoscopic endotracheal intubation by noting the degree of visibility of the faucial pillars and the uvula, with the patient seated, mouth wide open and the tongue fully protruded. Patients were classified into four classes according to the difficulty experienced in intubation (Fig. 5).

1. Class I—Clearly visible fauces, uvula, with a wide oropharynx—easy intubation.
2. Class II—Less clearly visible fauces and uvula, with a smaller opening of the oropharynx—intubation not as easy as in Class I.
3. Class III—Poorly visible fauces and uvula, with a small oropharynx encroached upon by the above structures—intubation could prove difficult. This preintubation evaluation correlated with the laryngoscopic visualization of the larynx—in Class I the larynx being well-visualized and in Class III, the larynx being poorly visualized. Samson and Young added a Class IV to Mallampati's classification.
4. Class IV—It is characterized by the inability to see the fauces, uvula and the oropharyngeal opening (patient seated, tongue protruded, mouth wide open). The vocal cords are not visualized on direct laryngoscopy, and intubation in these patients is generally unsuccessful.

In an emergency setting in the ICU, there is no time for elaborate preintubation evaluation. Patients requiring intubation are often hypoxic, restless, uncooperative and hemodynamically unstable. The simplest predictor of a likely successful intubation at the bedside in an emergency is the "Rule of Three". If the intensivist can place three finger breadths (6–7 cm) between the upper and lower teeth, between the mandible and the hyoid bone and between the thyroid cartilage and the sternal notch, intubation is usually successful.

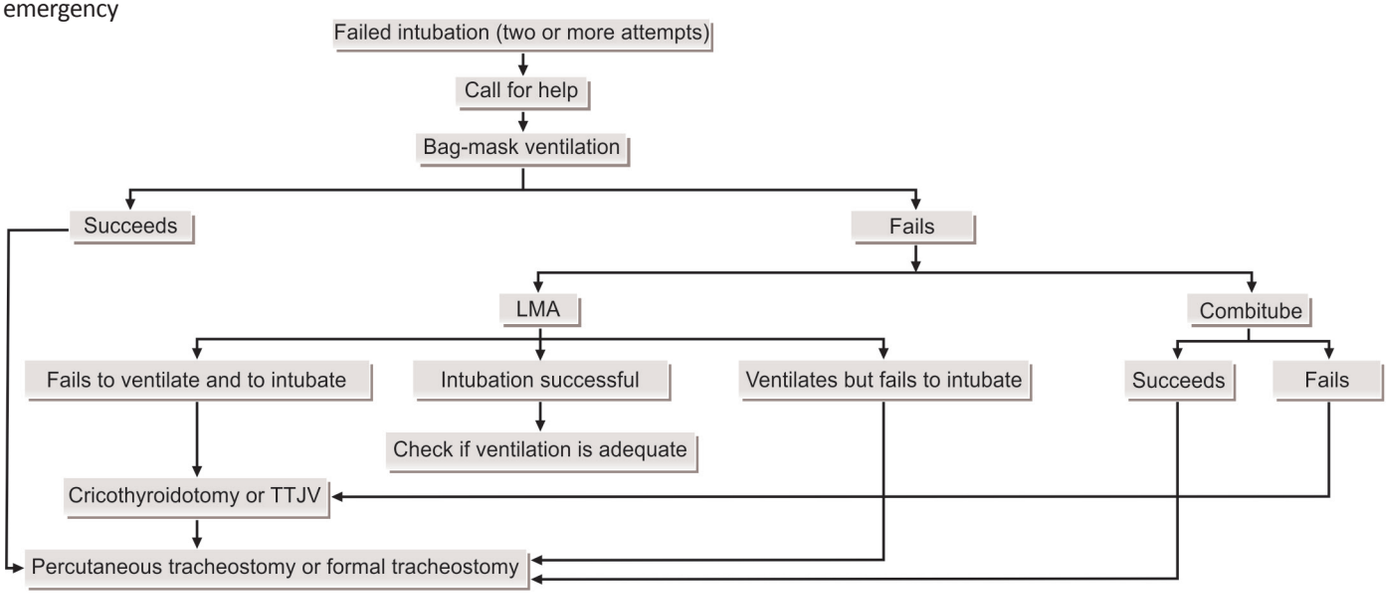
Difficult Intubation in the Critical Care Unit[3]

It is important not to make several attempts at intubation as this traumatizes the pharynx, larynx and makes a subsequent successful intubation doubly difficult. More than two attempts are associated with increased morbidity and an increased risk of cardiac arrest. Patients who are hypoxic are rendered even more hypoxic with all the attendant risks. Patients who to start with are hypotensive, hemodynamically unstable, or are in shock from any cause, or who are on vasopressors to maintain perfusion are at grave risk from preintubation death following repeated failed attempts at intubation. Sudden fluctuations in blood pressure and heart rate consequent to repeated attempts at intubation are dangerous in patients with aneurysms or in patients with unstable angina or myocardial infarction.

The management of failed endotracheal intubation attempts in a critical care setting should be considered under two heads—

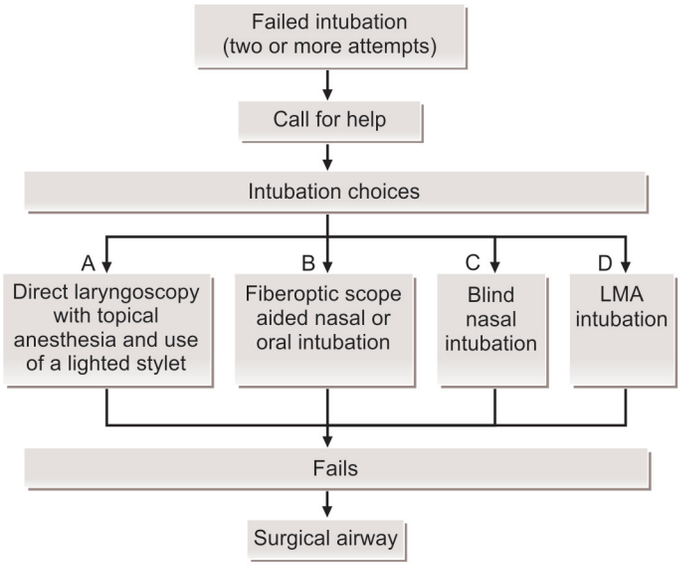
1. Failed intubation attempts in patients in whom securing an airway and establishing effective ventilation is a matter of extreme urgency, a matter of life and death, e.g. cardiac arrest, respiratory arrest, extreme obstruction to the airway (Flowchart 1).
   The following emergency measures need to be followed—
   - Call for help.
   - Continue bag-mask ventilation with 100% oxygen. Two individuals can perform this more effectively than one. One individual ensures that the mask fits tightly over the nose and mouth, preventing any air leak; the other squeezes the AMBU bag fed with 100% oxygen. The intensivist or physician should note whether the bag-mask ventilation is effective, as judged by good breath sounds over both lungs and by an oxygen saturation more than or equal to 90%. Difficulties in bag-mask ventilation are likely if any two of the following are present—age more than 55 years, edentulous patient, obesity (body mass index >26 kg/m^2), beard, history of snoring.
   - If a bag-mask ventilation fails or is ineffective, the situation is indeed very critical (cannot intubate-cannot ventilate scenario). Insert an LMA or even better (if available), an I-LMA and ventilate the patient via this airway. If the I-LMA is in place, attempt to intubate blindly using the specially designed endotracheal tube that goes with the I-LMA. Intubation (with a small-sized endotracheal tube) can also be attempted through a plain LMA with the aid of a fiberoptic bronchoscope. If effective ventilation through an LMA fails, and intubation via the LMA or via the I-LMA is unsuccessful, the quickest way of securing ventilation and preventing death from

Flowchart 1: Algorithm for the management of difficult airway and ventilation [in the intensive care unit (ICU)] in a life and death emergency



Abbreviations: TTJV, transtracheal jet ventilation; LMA, laryngeal mask airway.

Flowchart 2: Algorithm for the management of difficult airway and ventilation [in the intensive care unit (ICU)] in failed laryngoscopic attempts in less emergent situations



Abbreviation: LMA, laryngeal mask airway.

hypoxia, is by performing a cricothyroidotomy. A cricothyroidotomy should be promptly followed by an emergency percutaneous tracheostomy or by an emergency formal tracheostomy.

- Even if either bag-mask ventilation or ventilation through an LMA is successful, a more permanent and secure artificial airway is mandatory if spontaneous effective breathing has not returned. This is achieved either by a percutaneous tracheostomy or a formal tracheostomy. In expert hands, this can be performed within 10–15 minutes.
- If a preintubation clinical evaluation suggests that bag-mask ventilation or LMA ventilation cannot possibly be successful (as in extreme obstruction to the oropharynx, facial, neck injuries), proceed straight to a cricothyroidotomy, or a percutaneous tracheostomy, or a formal tracheostomy depending on the degree of the urgency of the situation.
- Transtracheal jet ventilation (TTJV) is an alternative to a surgical airway in a "cannot intubate-cannot ventilate" situation. After stabilizing the larynx, a 12–16-gauge catheter-over-needle (attached to a syringe partially filled with saline) is directed caudally through the cricothyroid membrane into the trachea. Tracheal entry is confirmed by aspiration of air bubbles. The catheter is now advanced (up to the hub), over the needle into the trachea with the aid of a small skin incision. The placement is confirmed by aspiration of air. The hub of the catheter is connected to a jet ventilation system. Care should be taken to stabilize the catheter and prevent any air leak at the incision site. We are not familiar with TTJV but it has been performed in all age groups and is the preferred surgical airway in children below 12 years. Airway obstruction below the larynx or complete upper airway obstruction can render expiration impossible and is a contraindication to TTJV. Complications with TTJV include subcutaneous emphysema, esophageal puncture, bleeding and barotraumas. TTJV is an emergency measure and is continued only till such time as a definitive airway has been secured.

2. Failed intubation attempts in situations which are emergent but which still allow some time to the intensivist for establishing an airway (Flowchart 2) . In the above

circumstance, the intensivist should use one or more of the other intubation techniques—

- Direct laryngoscopy with topical or local anesthesia (if topical anesthesia has not been already used).
- Use of a stylet, preferably a lighted one, to help guide the endotracheal tube into the trachea.
- A flexible fiberoptic scope to aid nasal or oral intubation.
- Blind nasal intubation.
- Intubation through an LMA.
- Retrograde intubation (in very rare circumstances).

Retrograde intubation is attempted by first puncturing the cricothyroid membrane with an 18-gauge introducer needle with catheter. A guidewire is threaded through the needle cephalad into the oropharynx and is then pulled out under vision using Magill's forceps. The guidewire is then placed directly in the lumen of the endotracheal tube. The latter is then guided along the guidewire through the glottis into the trachea. The guidewire is now pulled out through the proximal end of the endotracheal tube and the endotracheal tube fixed in proper position. This procedure requires practice and is more difficult than it appears; we have as yet never attempted retrotracheal intubation in our units.

TRACHEOSTOMY

A tracheostomy is in our opinion the most satisfactory artificial airway, particularly when the airway needs to be maintained for over 7–10 days. It completely bypasses the upper airway and the glottis, thus preventing any potential complications in that area. It causes less resistance to airflow (vis-à-vis the endotracheal tube), reduces dead space, allows easy and efficient suction of the tracheobronchial tree, and is easy to fix and stabilize. The conscious patient can eat freely, is not bothered by oropharyngeal secretions commonly observed with endotracheal tubes and tolerates the tracheostomy without undue discomfort. When performed by a skilled, experienced surgeon, the overall mortality (procedural with the tube in situ, or after removal) is around 1.5% (range 0–5%). This holds even when the procedure is done in critically ill patients.

Endotracheal Tube versus Tracheostomy

There is still a controversy as to when to continue with an endotracheal tube and when to opt for a tracheostomy. The decision to do a tracheostomy or persist with the endotracheal tube rests on the intensivist's perception of optimal patient care, available nursing care and the unit's experience and record of complications with each of the two artificial airways.

We prefer to do an elective tracheostomy after first intubating the patient, whenever we are convinced that the disease will necessitate the use of an artificial airway for more than 7 days. If it is difficult to gauge the time duration required for the artificial airway, we persist with the endotracheal tube for about 7–10 days, and then change over to a tracheostomy.

Probably each unit has its own preferences. We base our preferences on the fact that our unit has had few complications with tracheostomies, and that tracheobronchial toilet with suction of secretions is far easier through a tracheostomy than through an endotracheal tube. We have also noticed a significant incidence of subglottic edema and stenosis whenever an endotracheal tube has been in place for more than 10 days, prompting us to switch to a tracheostomy if we feel that an artificial airway is required beyond that period of time. However, there are many units in the West who persist with an endotracheal tube for as long as 3 weeks without encountering significant complications.

Complications of Tracheostomy[4]

It is to be noted that the three major emergencies associated with both tracheostomies and endotracheal tubes are—

1. Obstruction to the artificial airway.
2. Inadvertent extubation.
3. A major cuff leak.

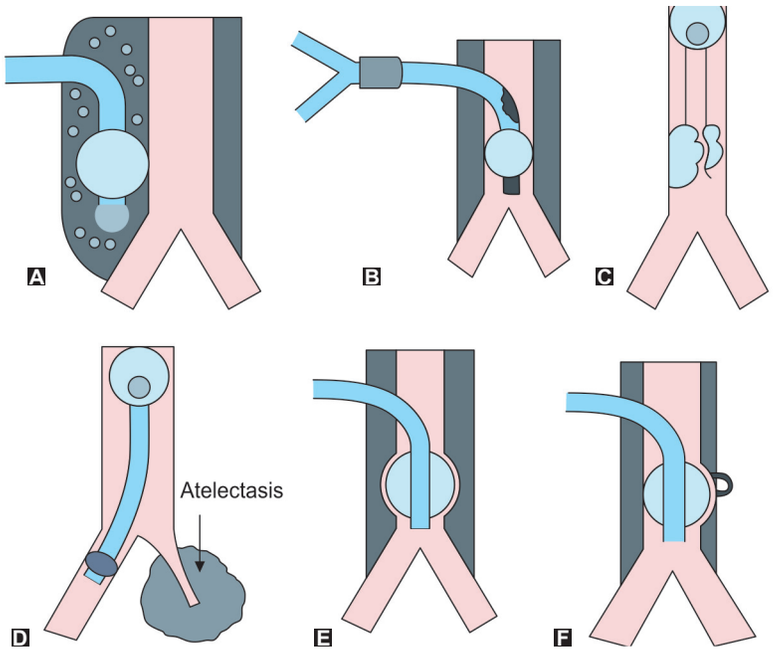
Obstruction Partial or complete obstruction of the tube by crusted inspissated secretions is perhaps the commonest and most important complication. A blocked tube can be disastrous if undetected or detected too late. Prevention of blockage by proper care of the artificial airway is vital.

Obstruction at times is observed below the lower end of the artificial airway. This is generally due to an overdistended cuff herniating over the lower end and blocking it. Prompt deflation of the cuff rapidly relieves the obstruction. Obstruction also occurs when the trachea below the cuff is partially clogged by inspissated mucus—a problem invariably due to inadequate humidification of inspired gas.

An endotracheal tube may sometimes be obstructed by a kink; slight manipulation of the head and neck should then restore patency. The bevel of the artificial airway may occasionally abut against the tracheal wall, carina or even bronchus, producing partial obstruction. This is relieved by gentle manipulation of the tube.

When faced with a possible obstruction to an artificial airway: (1) attempt to pass a suction catheter through the tube and note its passage—whether easy or obstructed; (2) deflate the cuff; (3) gently manipulate the tube. If none of these measures are effective, then the tube is promptly removed. Also, whenever there is a doubt about the exact cause of respiratory distress, as an ample measure of safety, the tube should be promptly changed. It is worth bearing in mind that an important cause of severe respiratory distress which resembles a blocked tube is a tension pneumothorax. A cardinal rule in the ICU is that a patient with an artificial airway must always have a duplicate artificial airway as also intubation and ventilation equipment at his bedside.

Inadvertent extubation This could prove disastrous if not urgently rectified in a patient on ventilator support who is paralyzed or heavily sedated. It abruptly cuts off ventilation, can produce serious surgical emphysema of the head, neck and chest as also mediastinal emphysema. If the endotracheal or tracheostomy tube lies above the vocal cords serious gastric distension can occur.



Figs 6A to F: Complications of tracheostomy. (A) Tube in pretracheal fascia-resulting in surgical emphysema of face and neck and sometimes of the mediastinum; (B) Blocked tube; (C) Overinflated cuff slipping over the end and blocking it; (D) Tube slipping into right main bronchus, preventing ventilation to the left lung; (E) Damage to trachea, either due to a very tight-fitting tube with an overinflated cuff, or injury to the posterior wall-end result, dilatation (as in the figure) or stricture and (F) Erosion of the posterior wall of the trachea, and rarely erosion of the innominate artery

Source: Udwadia FE. Diagnosis and Management of Acute Respiratory Failure. Mumbai: OUP; 1979.

Cuff leaks Cuff leaks are the least dangerous of the three artificial airway emergencies. A cuff leak can generally be compensated for by merely increasing the tidal volume in a patient on ventilator support. If this does not provide adequate ventilation, the airway will need to be changed.

OTHER COMPLICATIONS OF TRACHEOSTOMY (FIG. 6)

- *Ulceration with pressure necrosis of the trachea* Pressure of an inflated cuff or the tip of the tracheostomy tube may result in ulceration with pressure necrosis. The incidence of this is increased by the presence of an associated infection or the use of corticosteroids. In rare instances, the trachea may be perforated, and there is serious danger of erosion of a large vein or even the innominate artery, with severe bleeding and death resulting from aspiration of blood into the lungs.
- *Tracheal bleeding* Bleeding often occurs into and around the trachea, and within the wound in patients who have a bleeding tendency, particularly in the presence of hypoxia and hypercapnia. It takes the form of a capillary ooze, the main danger being of aspiration pneumonia and infection. Tracheal bleeding also occurs from pressure of the tube, especially when the tracheal mucosa has been rendered friable by repeated suction or infection. Exsanguinating bleeds are invariably due to perforation of a large vessel within the mediastinum.
- *Respiratory nosocomial infection* Infection is a serious and common complication. Prevention is by scrupulous asepsis during the performance of tracheostomy, and meticulous after-care of the tracheostomy. Every single tracheal aspiration should be considered as an aseptic surgical procedure, and should be performed with meticulous attention to detail. The mere growth of bacteria in tracheal aspirates is no evidence of active infection. Gram-negative organisms invariably grow from tracheal aspirates within a few days of a tracheostomy. The presence of fever, purulent secretions, leukocytosis and changing X-ray shadows determine the diagnosis of nosocomial infection (see Chapter Nosocomial Infections).
- *Mediastinal emphysema* This is invariably associated with surgical emphysema of the neck, and at times of the face and chest.
- *Tracheal stenosis* Tracheal stenosis is an important and dreaded complication of tracheostomy (Fig. 7). It can

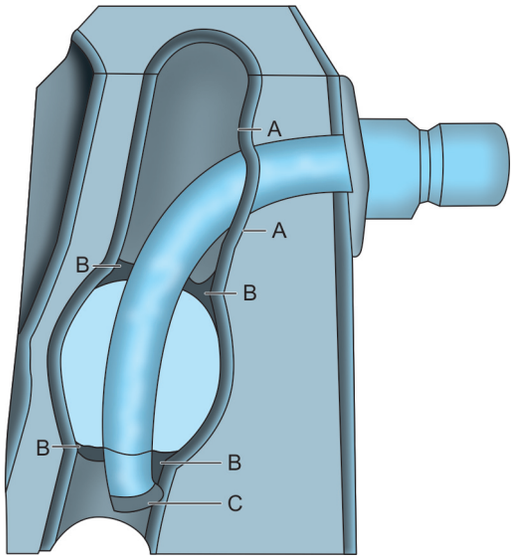


Fig. 7: Sites for occurrence of postextubation tracheal stenosis: (A) site of tracheostomy, (B) cuff site (the most common), (C) where tip irritates tracheal wall

occur anytime between 1 week and 2 years following tracheostomy. Post-extubation tracheal stenosis occurs at any one of the following three sites: (1) at the tracheostomy site, the incidence of this depends on the surgical technique; (2) at the cuff site: this is the commonest site for stenosis; (3) at the point where the tube tip irritates or damages the tracheal wall.

Conditions predisposing to tracheal stenosis include a high cuff pressure, prolonged ventilatory support over weeks or months, and hemodynamic instability with periods of poor perfusion which contribute to devitalization of the tracheal mucosa. Infection of the trachea, undue movement of the tracheostomy tube, or a tube tilted to one side so that its end irritates and produces pressure necrosis of a localized area of tracheal mucosa, are all contributory factors. Some workers have incriminated toxicity from chemical irritation produced by the tube material as an aggravating factor, particularly following ethylene chloride sterilization.

In over 1,200 tracheostomies performed, we have had only five patients with significant tracheal stenosis.

- *Tracheal dilatation* This occurs over the area of pressure exerted by the cuff, and can be prevented by proper cuff care.
- *Tracheomalacia* A softening of the trachea may occur following tracheostomy. This leads to inspiratory collapse of the trachea with obstruction of the airway following extubation.
- *Cardiorespiratory collapse* The association of cardiorespiratory collapse has been observed by us immediately following tracheostomy performed to relieve severe upper airways obstruction. It is generally seen when the tracheostomy is done on a patient who is in extremis. It does not occur if the airway has been first secured by an endotracheal tube, and the patient ventilated and oxygenated before doing a tracheostomy. Bendixen and his colleagues[5] believe that in patients with sudden severe airways obstruction, the hypoxia and hypercapnia produce a marked sympathetic stimulation with catecholamine liberation. If the sympathetic stimulus is suddenly removed, as after an emergency tracheostomy, then cardiovascular collapse may occur. In a similar fashion, if the respiratory drive produced by acute hypoxia and hypercapnia ceases, respiratory arrest can occur.

MAINTAINING THE ARTIFICIAL AIRWAY

It is not enough to establish and secure the airway. It is equally important to maintain, manage and care for the artificial airway if the hazards and complications involving the use of artificial airways are to be minimized.

Tracheostomy Care[6]

A high tracheostomy is always preferable as it enables the tip of the tube to lie well above the carina. It is best to use the largest tube that can be comfortably accommodated by the trachea. Small tubes should be avoided as they tend to get blocked, and they offer resistance to airflow. This is particularly unwelcome in those patients with acute respiratory failure who have well-marked airways obstruction, or who have a low compliance due to stiff lungs. The tube should have an even inflated cuff. High residual volume (low-pressure) cuffs should be always used; high-pressure cuffs have no place in modern respiratory care. Even when using high volume, low-pressure cuffed tubes, the cuff pressure should be checked daily and kept within acceptable limits. Excessive cuff pressures can induce tracheal injury and subsequent stenosis, particularly if the tracheostomy has been in use over several days or weeks. Salient points in tracheostomy care are given in Box 3.

SPECIAL CONSIDERATIONS IN AIRWAY MANAGEMENT[7]

Cervical Spine Injury[8]

A patient with polytrauma, who requires intubation should be presumed to have a cervical spine injury. In the absence of severe maxillofacial trauma or cerebrospinal rhinorrhea, a nasal intubation can be attempted. However, if urgent intubation is required as in the apneic or hypoxic patient, oral intubation should be done. During oral endotracheal intubation, a colleague or assistant should hold the neck in position, ensuring axial stability and preventing any flexion or anterior movement of the neck for fear of damaging the spinal cord.

Increased Intracranial Tension

Intubating patients with head injury who have a rise in intracranial pressure may be difficult for several reasons—change

Box 3: Salient points in tracheostomy care

Use sterile gloves for handling tracheostomy tube

- Care of cuff—
  - Use minimal occluding volume for inflating cuff—minimal leak techniques
  - Measure cuff pressure daily, and keep this within acceptable limits (14–24 cm H_2O)
  - Deflate cuff periodically, except when this is contraindicated for specific reasons
- Care over suction of secretions—
  - Use "no-touch" sterile technique
  - Preoxygenate (with high FiO_2) in a hemodynamically unstable patient before suction
  - Do not suck for more than 10 seconds
  - Do not use a very large bore catheter for suction
  - If possible, suck through an adaptor so that ventilator support on high-flow O_2 is not interrupted
  - Stop suction if bradycardia or hypotension occur; increase FiO_2 to 100% for a short time
  - Liquefy viscid secretions; use physiotherapy
  - Humidify inspired gas
- Care of tracheostomy tube—
  - Ensure that tube is central in position and does not tilt or slip into one bronchus
  - Ensure that tube does not get blocked
  - Change tube every 4–7 days
- Care of tracheostomy wound:
  - Use sterile dressing and antibiotic ointment
  - Be alert to possible complications of tracheostomy

in mental state, difficulty in opening the mouth, associated facial trauma. Further rise in intracranial pressure should be avoided as far as possible during intubation. Also, cervical spine trauma should always be suspected in a patient with head injury. The anesthetic agent used for intubating these patients should ideally preserve cerebral perfusion, and lower cerebral blood volume while maintaining hemodynamic stability. Thiopental offers neuroprotection but cerebral hypoperfusion may result from its depressant effect on the myocardium and because of peripheral vasodilatation. Etomidate is preferred in hemodynamically unstable patients. If a neuroparalytic agent needs to be used for intubation, vecuronium (0.25 mg/kg) or rocuronium (1.2 mg/kg) is to be preferred.

In patients with polytrauma including head injury with raised intracranial pressure, it may at times be impossible to perform a laryngoscopic endotracheal intubation. The airway may need to be secured by alternative means.

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CHAPTER 31

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are in-built features in the natural history of the disease, punctuating its course from time-to-time. They significantly increase both morbidity and mortality, the in-hospital mortality of COPD exacerbations being as high as 10%. In the UK, COPD exacerbations are the most common cause of medical hospital admissions, amounting to 15.9% of the hospital admissions at a huge cost to the national exchequer. In large metropolitan cities in India, COPD exacerbations are an important and frequent cause of admission to critical care units. Approximately, 1 in 15 patients reporting to the emergency department in a busy Mumbai hospital comes with worsening of symptoms of COPD.

Acute exacerbations are more frequent and often more severe in patients with increasing severity of COPD. The annual frequency of exacerbations in different patients having the same severity of COPD varies for unknown reasons. Predisposition to acute exacerbations may well be related to increasing severity of the disease, greater inflammation of the small airways, greater exposure to and perhaps greater susceptibility to infection and to the presence of lower airways bacterial colonization.

Definitions

An acute exacerbation of COPD is an acute worsening of symptoms associated with worsening lung functions that could in some patients precipitate acute respiratory failure (ARF) or the acute worsening of chronic respiratory failure. Respiratory failure (acute or acute on chronic) is often the culminating feature of an acute severe exacerbation of COPD. It is important to stress this fact as it entails an awareness for diagnosing this event and necessitates expert critical care in management.

The guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) define an exacerbation as an event in the natural course of the disease characterized by a change in the patient's dyspnea, cough and/or sputum that is beyond day to day normal variations, is acute in onset and may warrant a change in medication in a patient with underlying COPD.[1]

PATHOPHYSIOLOGY[2,3]

Acute exacerbations are associated with increased inflammation within the peripheral airways and the lungs. Clinically, this is manifested by worsening dyspnea and sputum production.

Pathological features include an even more intense inflammatory exudate and edema of the mucosa of the peripheral airways, an increase in tone of the bronchial muscle and increased mucous production. The acute increase in obstruction to the airways and the further increase in airflow limitation, if sufficiently severe, produce dynamic hyperinflation. Dynamic hyperinflammation is the mechanism responsible for progressive air-trapping within the alveoli leading to a progressive increase in the intra-alveolar pressure and the functional residual capacity (FRC). It can occur with frightening rapidity during an acute exacerbation of COPD. The underlying cause is airways obstruction and airflow limitation. A dynamic compression and collapse of the peripheral airways during expiration leads to a reduced rate of lung emptying. In these circumstances, an inspiratory effort starts before the prolonged expiration is complete. Air is

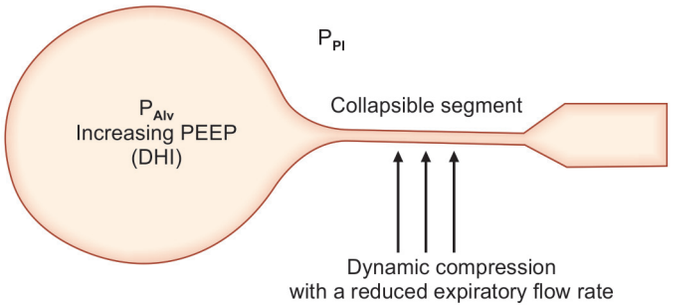


Fig. 1: Dynamic compression of the airways during expiration resulting in dynamic hyperinflation (DHI)
Abbressions: P_{Alv}; intra-alveolar pressure, P_{pl}; intra-pleural pressure.

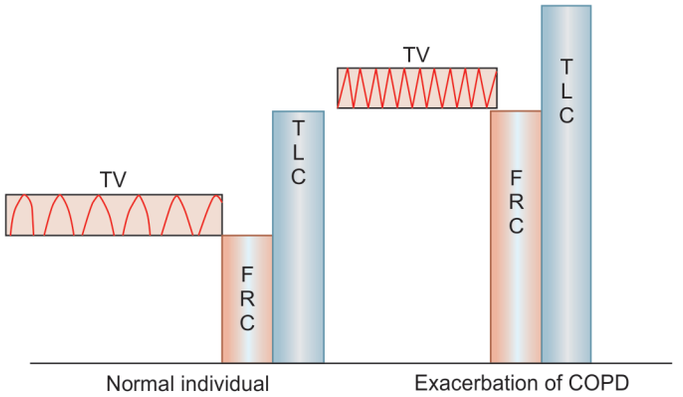


Fig. 2: Increased functional residual capacity (FRC) with the patient breathing at higher lung volumes in severe chronic obstructive pulmonary disease (COPD)

thus trapped in the alveoli causing a rise in the intra-alveolar pressure. The end-expiratory alveolar pressure continues to rise every time a prolonged expiration is prematurely cut short or interrupted by an inspiration. This progressive rise in end-expiratory alveolar pressure is termed intrinsic PEEP or auto-PEEP; it results in an increase in the FRC and in overinflated lungs (Figs 1 and 2).

Dynamic hyperinflation exerts a deleterious effort on the respiratory and circulatory systems—

- Breathing at higher lung volumes is greatly uncomfortable and causes increasing distress. The work of breathing is significantly increased because of an overinflated chest. An overinflated chest has ribs which are more horizontally placed; also the length-tension relationship of the intercostals muscles is far from optimal so that the chest bellows work at a mechanical disadvantage. The low diaphragm and the decreased area of apposition between the diaphragm and the chest wall are further mechanical disadvantages adding to the work of breathing.
- Though it would appear that the expiratory muscles need to work hard because of expiratory obstruction to the airways and expiratory airflow limitation, it is in fact the inspiratory muscles that endure a great workload. This is because with each inspiration the inspiratory muscles need to contract strongly and generate a sufficiently negative intrapleural pressure so that the collapsed peripheral airways are pulled open and the pressure in the central airways and alveoli is rendered subatmospheric, to enable inspiratory air flow to occur. This increased work of inspiratory muscles is required when they are for reasons stated above working at a mechanical disadvantage. Therefore, when dynamic hyperinflation is marked (as in an acute exacerbation of COPD), inspiratory muscle fatigue occurs, and may lead to a respiratory arrest (Fig. 3).
- Increasing dynamic hyperinflation is often associated with hypoxia and hypercapnia because of ventilation-perfusion inequality and alveolar hypoventilation (Flowchart 1).
- The markedly hyperinflated lungs associated with severe dynamic hyperinflation squeeze the capillaries in the functioning and perfused alveoli, resulting in an increased pulmonary vascular resistance and precipitating pulmonary hypertension and right heart failure in patients with moderate to severe COPD. Hypoxia and hypercapnia also cause pulmonary vasoconstriction and contribute further to pulmonary hypertension.

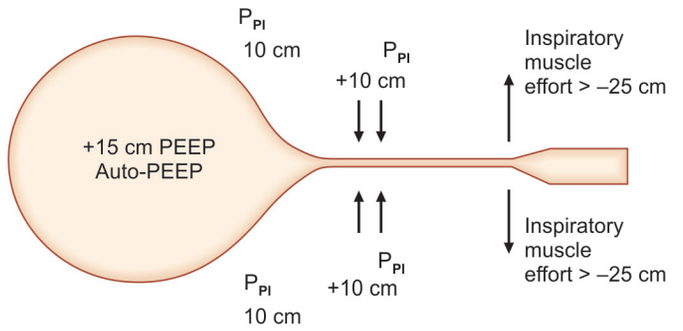
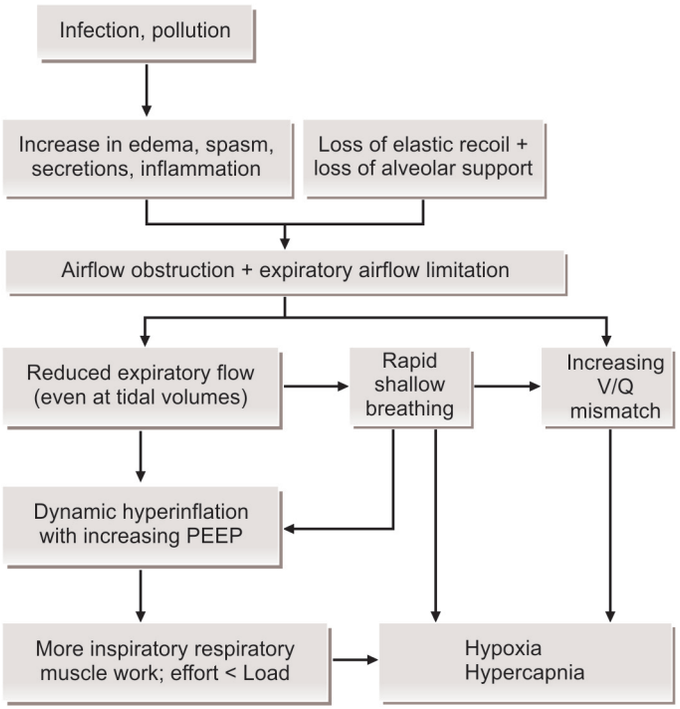


Fig. 3: An increased inspiratory effort is necessary to open collapsed airways and produce a sufficient negative intrapleural pressure to overcome the positive intra-alveolar pressure so as to allow inspiratory air flow. During expiration, the intrapleural pressure of +10 cm H_2O prematurely closes the airways. Total intra-alveolar pressure is 25 cm H_2O. During inspiration, the inspiratory muscles must create a negative intrapleural pressure of well over –25 cm H_2O to allow inspiratory airflow

Severe dynamic hyperinflation is associated with well marked rise in the positive end-expiratory pressure (auto-PEEP). This hinders venous return and causes hypotension. When the auto-PEEP is very marked, it exerts an effect similar to that seen in cardiac tamponade (caused by a large pericardial effusion). Severe dynamic hyperinflation with very high auto-PEEP can cause cardiac arrest. Hyperinflated lungs with increase in auto-PEEP can cause barotrauma. Spontaneous pneumothorax is the commonest result of barotrauma. Mediastinal emphysema and interstitial emphysema are two other complications resulting from barotrauma.

Marked hyperdynamic inflation is classically seen in patients with severe exacerbations of COPD, or in patients in a crisis who are incorrectly ventilated. End-stage COPD is also often associated with progressive dynamic hyperinflation.

Flowchart 1: Pathophysiology of acute respiratory failure (ARF) in exacerbation of chronic obstructive pulmonary disease (COPD)


Infection, pollution
Increase in edema, spasm, secretions, inflammation
Loss of elastic recoil + loss of alveolar support
Airflow obstruction + expiratory airflow limitation
Reduced expiratory flow (even at tidal volumes)
Rapid shallow breathing
Increasing V/Q mismatch
Dynamic hyperinflation with increasing PEEP
More inspiratory respiratory muscle work; effort < Load
Hypoxia
Hypercapnia

As has been already explained, dynamic hyperinflation in acute severe exacerbations can occur with frightening rapidity, the patient becoming increasingly uncomfortable and dyspneic, because he has to breathe at progressively high lung volumes. The work of breathing is substantially increased, well beyond what it was prior to the exacerbation, and there is further impairment of respiratory muscle function. The effort expended by the chest bellows and the respiratory muscles is not commensurate with the extra load of breathing. This results in alveolar hypoventilation and hypercapnic respiratory failure. Hypoxia is also worsened in severe exacerbations because of increasing ventilation-perfusion inequality.

Not all acute exacerbations are severe, the degree of exacerbation being probably dependent on the degree of small airways inflammation present in the stable state.

Moderate and severe COPD (Grade III, Grade IV) is associated with a greater degree of inflammation of the small airways, when compared to Grade I and Grade II COPD. This may well be the reason why acute exacerbations are generally more severe in patients with Grade III, Grade IV COPD.

ETIOLOGY[2]

The commonest cause of an acute exacerbation in COPD is infection. The common bacteria causing infective exacerbations are *Streptococcus pneumoniae*, *H. influenzae*; in older patients, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are often the infecting agents. There is growing incidence of *Moraxella catarrhalis* as a causative infective agent, both in the West and the developing world. Molecular biology using polymerase chain reaction (PCR) techniques has provided evidence for an increasing role of viruses in the etiology of acute exacerbations. The commonest responsible virus is the rhinovirus. Other viruses include the respiratory syncytial virus, coronavirus, influenza virus and the adenovirus. The role of atypical organisms, in particular mycoplasma and chlamydia is unclear.

Acute exacerbations have also been noted to occur following an acute increase in indoor pollution, exposure to increased outdoor pollution, and due to sudden increase in exposure to an occupational risk factor. One reason for increased incidence of exacerbations during winter is excessive outdoor pollution which blankets large cities in India at almost ground level. Exposure to pollution from exhausts of cars in traffic jams can lead to acute exacerbations, and is another reason for the emergency visits to hospitals. A sudden and marked spurt in the number of cigarettes smoked has been known to cause an acute exacerbation of COPD. The common organisms and pollutants responsible for acute exacerbation of COPD are listed in Box 1.

Clinical Features (Box 2)

An acute exacerbation of COPD is characterized by a clear worsening of respiratory symptoms, well beyond what the patient is used to experiencing. These symptoms chiefly include increased dyspnea, increased cough with an increase in sputum volume, purulent sputum and an increase in wheeze.

Physical findings include all the features observed with airways obstruction and airflow limitation. Tachycardia, tachypnea, excessive use of accessory muscles of respiration,

Box 1: The common organisms and pollutants responsible for acute exacerbation of COPD

- Bacteria—
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Moraxella catarrhalis*
  - *Pseudomonas aeruginosa*
- Viruses—
  - Rhinovirus
  - Influenza
  - Parainfluenza
  - Coronavirus
  - Adenovirus
  - RSV
- Atypical bacteria—
  - *Chlamydia pneumoniae*
  - *Mycoplasma pneumoniae*
- Common pollutants—
  - Nitrogen dioxide
  - Particulates
  - Sulfur dioxide
  - Ozone

Abbreviations: COPD, chronic obstructive pulmonary disease; RSV, respiratory syncytial virus.

Box 2: Clinical features of acute severe exacerbation of COPD

- Increase in dyspnea, cough, sputum
- All the clinical features of severe airflow limitation
- Features of hypoxia and hypercapnia
- Features of right heart failure may be present

Abbreviation: COPD, chronic obstructive pulmonary disease.

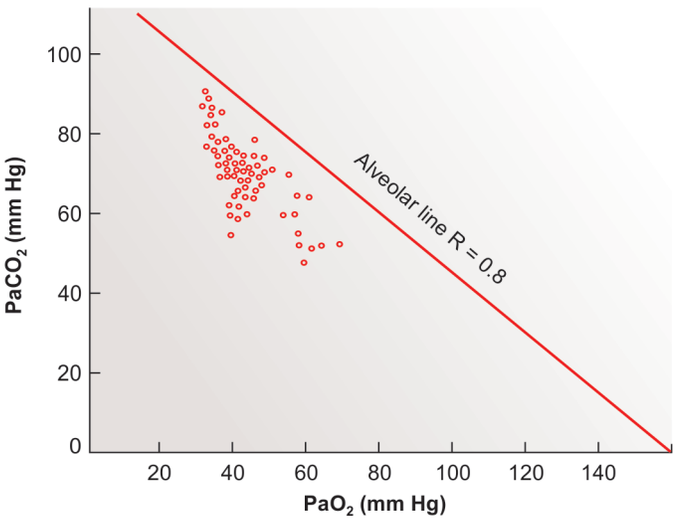


Fig. 4: Arterial blood gas (ABG) in 64 patients with Grade III–Grade IV chronic obstructive pulmonary disease (COPD) who developed an acute exacerbation of COPD. Note severity of hypoxemia and hypercapnia present in most patients with Grade III–IV COPD in an acute severe exacerbation

Source: Udwadia, FE. Diagnosis and Management of Acute Respiratory Failure. Oxford, Delhi, Mumbai: Oxford University Press; 1979.

in-drawing of intercostal spaces during inspiration with paradoxical breathing are all seen in severe exacerbations. Expiration is clearly prolonged and there is an audible wheeze. Rapidly increasing dynamic hyperinflation will cause an actual measurable increase in the circumference of the chest, increasing tachycardia, hypotension, marked distress and difficulty in breathing, the breath sounds ultimately being reduced to short gasps. Auscultation in the presence of rapidly progressive dynamic hyperinflation may reveal faint or absent breath sounds, the expiratory wheeze often being inaudible. Periods of apnea may interrupt the breathing which is often irregular. Central cyanosis may be evident because of increasing hypoxia. Hypercapnia may progressively worsen, leading often, though not always to flapping tremors and confusion. Rhythm disturbances may occur in the form of multiple atrial or ventricular extrasystoles, supraventricular tachycardia, chaotic atrial tachycardia, atrial fibrillation and even ventricular tachycardia.

Severe acute exacerbations can precipitate right heart failure, particularly in patients with Grade III and Grade IV COPD (Fig. 4). This is related to pulmonary vasoconstriction and pulmonary hypertension caused by acute hypoxia and hypercapnia in an individual who often has a baseline increase in pulmonary vascular resistance due to inflammatory changes in the small airways, periphery of the lungs and the pulmonary vessels. The most important and early sign of right heart failure in COPD patients is edema of the feet for which there is no other obvious cause. The edema can worsen and can be so marked as to be generalized. In severe exacerbations in Grade III and Grade IV COPD, electrocardiography (ECG) shows a P pulmonale often associated with clockwise rotation. There may be evidence of right ventricular enlargement and/or a right bundle branch block pattern. These ECG findings are acute, for they generally regress after recovery and often return to a stable state. Echocardiography may corroborate right ventricular systolic dysfunction, some degree of functional tricuspid incompetence and pulmonary hypertension.

Acute exacerbations of COPD are not necessarily severe; some are indeed mild, easily manageable at home. Apart from a worsening of symptoms more than what is usual for the patient, physical signs are limited to those caused by a modest increase in airways obstruction and airflow limitation. The duration of acute exacerbations varies. Milder exacerbations often treated at home may be relieved within 4–7 days with adequate treatment, though full recovery with return to baseline symptoms may take as long as 3–4 weeks in some of these patients. Recurrence rate varies in different individuals for unclear reasons. In a cohort of patients with moderate to severe COPD followed up after acute exacerbation, 22% suffered a recurrence within 50 days of the first (index) exacerbation. Perhaps an initial exacerbation may well increase susceptibility to a subsequent one.

Box 3: Causes of hypoxemia

- V/Q mismatch causing an increased alveolar arterial O_2 gradient
- Alveolar hypoventilation
- Small shunts amounting to 4–10% of the cardiac output
- Low PvO_2 (observed in some patients with cor pulmonale and severe heart failure)

Abbreviation: V/Q, ventilation/perfusion.

Box 4: Causes of hypercapnia

- Alveolar hypoventilation due to increased load and the inability of the respiratory muscles (inspiratory in the main) to meet this load. Inspiratory work of breathing is doubled in acute respiratory failure (ARF); increase in auto or intrinsic PEEP accounts for more than half of this increase in the work of breathing
- V/Q mismatch
- Change in the pattern of breathing—smaller tidal volume with an increase in respiratory rate. This may be an adaptive mechanism to avoid increasing ventilation and respiratory muscles activation to the point where muscle fatigue ensues

Abbreviation: V/Q, ventilation/perfusion.

The causes of hypoxemia and hypercapnia in an acute exacerbation of COPD are listed in the Box 3 and Box 4 respectively.

Investigations

Investigations are done with three objectives in mind—

1. To determine the severity of the exacerbation.
2. If infection is the cause, to determine if possible the infective agent responsible for the exacerbation.
3. To exclude other complications which can cause an acute respiratory crisis in COPD; a crisis that may be clinically indistinguishable from that caused by an acute exacerbation of COPD.

Investigations include a routine complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). The latter is believed to be an important marker for the presence and degree of the underlying inflammation in the peripheral airways. X-ray chest and ECG are always done routinely. O_2 saturation, arterial blood gases (ABGs), and pH are vital tests. The O_2 saturation will serve as a guide to the degree of hypoxia, but it is often impossible to diagnose the presence and degree of CO_2 retention without actually determining the partial pressure of carbon dioxide in the blood. In severe exacerbations causing ARF or acute on chronic respiratory failure, arterial pH is of vital importance. An arterial pH less than 7.25 is perhaps the most important single factor associated with high mortality.

In severe exacerbations, it is important to determine the baseline function of organ systems. Serum creatinine, blood urea nitrogen (BUN) levels and serum electrolytes need to be done. Sputum microscopy and culture may help (though not necessarily so) in arriving at the organism responsible for an acute infective exacerbation. It is of particular help if *P. aeruginosa* or *K. pneumoniae* are grown on culture, as this will dictate the correct choice of antibiotics.

Spirometry is not useful in severe exacerbations as the patient is too ill to allow reliable results. Also, baseline spirometric readings of a patient admitted in an emergency are not generally available.

PROBLEMS IN DIAGNOSIS

Problems in diagnosis are not infrequent in patients who on clinical examination appear to have an acute exacerbation of COPD. The major difficulty encountered is to distinguish left ventricular dysfunction and failure in a patient with COPD from an acute severe exacerbation of COPD. This difficulty is compounded when acute left ventricular (LV) failure is the sole manifestation of ischemic heart disease (IHD), without a preceding history of anginal pain and without clear evidence of ischemia on the ECG. Both COPD and IHD often manifest in similar age groups. Interestingly, patients with COPD who develop acute LV failure often present with tachypnea and marked wheezing rather than the usual crackles of pulmonary edema. An X-ray chest may be unhelpful and in fact misleading, because occasionally predominantly unilateral pulmonary edema may be seen in COPD patients who develop acute LV failure. The unilateral pulmonary edema is often misdiagnosed as pneumonia. Investigations are often noncontributory. We have found echocardiography notoriously unreliable and even misleading in the diagnosis of diastolic dysfunction in acute LV failure.

A case history illustrates this well. Mr S, a heavy cigarette smoker with Grade III–Grade IV COPD was admitted with classic features of an acute exacerbation of COPD due to an acute pulmonary infection. He went into ARF with severe hypoxia, hypercapnia and respiratory-cum-metabolic acidosis. Medical management including noninvasive ventilator support failed to help. He was intubated and put on mechanical ventilator support. He could not be weaned off support for over 10 days. Every night there was a crisis characterized by sudden tachypnea so that he would clash with the machine. There was marked bronchospasm during tachypneic spells, no change in the X-ray chest, with the central venous pressure (CVP) remaining within the normal range. A tracheostomy was done and ventilator support continued. One night he had an exceptionally severe bout of tachypnea with marked wheezing and increased desaturation, requiring a significant step-up in the fraction of inspired oxygen (FiO_2). On this occasion, the tracheal aspirate was frothy and copious, pointing to pulmonary edema. LV failure due to IHD was diagnosed. A coronary angiography showed a tight stenosis in the proximal left anterior descending artery. An angioplasty with stenting was performed. The patient

Box 5: Problems in diagnosis

- Association of LV dysfunction and failure in patients with COPD
- Complication of pulmonary embolism in a patient with COPD
- Complication of a pneumothorax in a patient with COPD
- Pneumonia, atelectasis, presenting with acute respiratory failure (ARF)
- Acute severe asthma
- Non-respiratory causes triggering ARF in COPD

Abbreviations: LV, left ventricular; COPD, chronic obstructive pulmonary disease.

could be weaned off the ventilator support within the next 2 days. It is now 5 years since the episode. He is on continuous oxygen therapy and has a reasonable quality of life.

Pulmonary embolism complicating COPD can also mimic an acute exacerbation. Here again when pulmonary embolism occurs in a patient with COPD, breathlessness is invariably associated with severe wheezing. A negative D-dimmer test is a strong point against pulmonary embolism. When in doubt, a pulmonary angiography should be done.

Acute pneumonia, lobar atelectasis due to mucus plugging, are other pulmonary pathologies that can precipitate severe acute respiratory failure. The clinical diagnosis may be missed as an acute exacerbation of COPD causing ARF.

Even a shallow pneumothorax in a patient with moderate to severe COPD can induce ARF. This is because an overinflated lung (as occurs in COPD) does not easily collapse even with a good-sized pneumothorax. The pressure within the pneumothorax may be high but it appears quite shallow on the X-ray. This is one reason why any patient with a diagnosis of acute exacerbation of COPD admitted to the hospital, or reporting to the emergency department, should always have an X-ray chest done. It is almost impossible to clinically detect a shallow pneumothorax in a patient with COPD. The only reliable sign is diminished breath sounds over the area of the pneumothorax, but unequal breath sounds over both lungs are not uncommon in COPD, even without pneumothorax.

It is obvious that each of the three complicating conditions listed above can worsen lung function in patients with COPD. This is because each of these conditions will cause tachypnea. Tachypnea in moderate to severe COPD is often characterized by an expiration which is incomplete, being interrupted by the next inspiration. This will lead to progressive air-trapping, hyperinflated lungs with all the consequent deleterious effects on the work of breathing.

Acute severe asthma may in the absence of a good history be difficult to distinguish from an acute severe exacerbation of COPD when the patient is seen for the first time in an emergency. In fact some severe asthmatics have very poor reversibility in airways obstruction and airflow limitation, exactly resembling patients with COPD. Fortunately, the management remains exactly the same.

Box 6: Conditions other than acute exacerbation of COPD which are known to precipitate an acute respiratory crisis in COPD patients

- Respiratory conditions—
  - Pneumonia
  - Pulmonary atelectasis
  - Pneumothorax
  - Pleural effusion
  - Pulmonary thromboembolism
  - Sputum retention from any cause
- Non-respiratory conditions—
  - Acute left ventricular failure
  - Use of respiratory depressants, drugs, tranquilizers
  - Postoperative conditions
  - Trauma (fracture ribs, fracture femur)
  - Systemic infections
  - Severe blood loss

Abbreviations: COPD, chronic obstructive pulmonary disease.

A number of other complications occurring outside the respiratory system may produce an acute respiratory crisis with respiratory failure in patients with well-marked Grades III and IV COPD. For example, narcotic drugs, anesthetics, sedatives, tranquilizers even in small doses can depress the ventilatory drive sufficiently to lead to increasing hypercapnic respiratory failure and a mistaken diagnosis of acute exacerbation of COPD. Trauma causing rib fractures or fractures of the femur, acute systemic infections and sputum retention from any cause are other complications that cause an acute respiratory crisis in COPD patients.

It is therefore, a cardinal principle in medicine that if a patient with well-marked COPD develops ARF or acute on already existing chronic respiratory failure, a careful search for all possible causes must be made. An acute exacerbation of COPD is an important and common cause for the above scenario, but it certainly is not the only cause (see Boxes 5 and 6).

MANAGEMENT[4]

The principles in the management of an acute exacerbation of COPD are—

- Relief of airways obstruction and airflow limitation through a more intensive use of inhaled bronchodilators.
- Use of corticosteroids to reduce the increased inflammation within peripheral airways and lung parenchyma.
- Use of antibiotics in the presence of bacterial infection.
- Use of oxygen to relieve dyspnea and most importantly to relieve hypoxia.
- Use of ventilatory support in patients who are in acute respiratory failure or in acute on chronic respiratory failure in spite of conservative treatment mentioned above.
- Treatment of right heart failure.

We consider the role of the physiotherapist invaluable in patients who have a great deal of sputum but are unable to expectorate it.

Treatment is tailored to the degree of severity of the acute exacerbation. Mild exacerbations may just need intensified bronchodilator therapy. If the sputum is purulent, antibiotics need to be given after collecting sputum for culture or sensitivity but without waiting for the results. If the exacerbation seems more than mild, corticosteroids need to be administered. Controlled oxygen is given for the relief of both hypoxia and dyspnea. It is the first important therapeutic measure in hypoxic patients, and should be started promptly in a patient admitted with ARF. Persistence or increasing respiratory failure in spite of conservative management necessitates the use of ventilator support. Noninvasive ventilator support is preferable, but invasive ventilator support should not be delayed if indications so exist.

Inhaled Bronchodilator Therapy[5]

Mild exacerbations of COPD are often controlled merely by increasing the frequency of inhaled bronchodilators. Both short acting β2-agonists and an anticholinergic-ipratropium bromide can be used, preferably through a spacer device, though there is no evidence that the use of both is more effective than the use of either one or the other. Severe exacerbations necessitate the administration of levosalbutamol (1.25 mg 8-hourly) and an anticholinergic agent like ipratropium (500 mcg 8-hourly) through a nebulizer, even though again there is no evidence that this is superior to the use of a metered dose inhaler with a spacer device. Patients in our part of the world who come in with an acute severe exacerbation may have never used a metered dose inhaler and find it impossible to do so effectively at this juncture. Women in particular find it difficult to use the metered dose inhaler even when the COPD is stable. Patients with severe exacerbations are extremely dyspneic, have a poor inspiratory effort and very small tidal volumes. Very little of the drug reaches the airways in spite of using a volume spacer with the metered dose inhaler. The relief in dyspnea due to reduced airways obstruction following a switchover from a metered dose inhaler with a spacer device to the nebulized administration of the drugs, is at times too obvious to be disbelieved.

The frequency of nebulization of salbutamol is generally three times a day, perhaps repeated once in the middle of the night if necessary.

Theophylline

Oral theophylline should be given or continued (if the patient is already on the drug) for its bronchodilator effect in the milder forms of acute exacerbation of COPD. In the more severe forms of acute exacerbation, intravenous (IV) aminophylline 0.25 g to at the most 0.75 g intravenously over 24 hours through an infusion pump may be given, particularly when there is marked bronchospasm. Great care must be taken particularly in patients who have received oral theophylline during the stable phase of COPD. Theophylline levels in the blood should be carefully monitored and should not exceed 15 mg/dL.

Use of Corticosteroids[6]

Systemic corticosteroids are indicated in all except the very mild exacerbations that respond well to inhaled bronchodilator therapy alone. A number of randomized trials indicate that the use of steroids relieves airways obstruction producing a rapid improvement in forced expiratory volume in one second (FEV_1). Other outcome effects such as hospitalization, length of hospital stay, and oxygenation are variable. Their effect on mortality has not been determined. Corticosteroids act through their anti-inflammatory effect. The generally accepted dose is 40 mg prednisolone orally for 10–14 days. Critically ill patients or those in whom absorption of the drug is suspect because of vomiting should be given methyl prednisolone 40 mg 8-hourly intravenously till improvement occurs, following which oral prednisolone is used. Nebulized budesonide (0.5 to 1 mg nebulized twice daily) also acts through its direct anti-inflammatory effect on the airways. It is however difficult to ascertain to what extent the drug reaches the peripheral airways, where inflammation is most marked. In severe exacerbations, budesonide should not substitute the use of systemic corticosteroids.

Antibiotics[7,8]

Antibiotics should be used whenever the sputum is purulent—colored yellow or green. These patients should be given antibiotics promptly without awaiting culture sensitivity reports. The choice of antibiotics depends on the organism generally prevailing in patients with acute exacerbation of COPD in a particular locale. The antibiotics used should cover the common organisms generally responsible for acute exacerbations—*S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. In elderly individuals, Gram-negative infections are not uncommon, particularly those due to *P. aeruginosa* and *K. pneumoniae*. An appropriate cover for Gram-negative infections is then necessary. Viral infections (the rhinovirus in particular) are being increasingly recognized as a cause of acute exacerbations of COPD. Antibiotics are of no use when this is so.

The question often arises—does one use empiric antibiotic therapy in patients with severe acute exacerbation, particularly in those with ARF, when there is no evidence of bacterial infection? Rightly or wrongly, we do so, as some patients who have infection may have no sputum and the danger of not treating a possible infection in such critically ill patients, particularly when they are old and feeble is great. When such patients need intubation and ventilatory support, suction through the endotracheal tube has often revealed dirty yellow or green tracheobronchial secretions. Interestingly, a meta-analysis of six sufficiently well-designed randomized trials by Saint and colleagues[7]

confirmed a statistically significant benefit that favored the use of antibiotics. Duration of antibiotic therapy is generally not more than 4–7 days.

Controlled Oxygen Therapy[2,5,9,10]

Oxygen through nasal prongs or a Venturi mask is used to relieve dyspnea, but most importantly to relieve hypoxia. Patients with Grade III, IV COPD who develop a severe acute exacerbation are invariably hypoxic and often hypercapnic. The PaO_2 very often is less than 55–60 mm Hg. These patients always need oxygen and are at risk of death from worsening hypoxia. *It should be a cardinal rule to administer oxygen immediately, and as the very first measure in any acutely ill patient with COPD*. Oxygen should be administered in a controlled manner and should be carefully supervised. Uncontrolled oxygen therapy can be lethal in these patients. Intensive care is crucial for survival. The objective is to increase PaO_2 to a safe level of 60 mm Hg or ensure an oxygen saturation of 90%, without the arterial pH falling below 7.25. Controlled oxygen therapy can be given through a Venturi mask, which allows an FiO_2 of 24%; this can be increased through Venturi masks that allow an FiO_2 of 26% or even 28–30%, or more, if dangerous hypoxia is unrelieved. Oxygen given through nasal prongs at a flow rate of 1–2 L/minute is a cheap, convenient and effective alternative, as this generally equates to an FiO_2 of 24%.

The response to controlled oxygen therapy (starting with an inspired oxygen content of 24%, and increasing to 26% or even 28–30% if dangerous hypoxia is unrelieved), falls into the following three patterns—

1. Relief of hypoxemia, with a fall in the $PaCO_2$ and an overall clinical improvement.
2. Relief of hypoxemia, but an initial increase in the $PaCO_2$ with a further fall in arterial pH to not less than 7.25. The $PaCO_2$ then steadies at a higher level, or returns to pretreatment levels. After a couple of days, the $PaCO_2$ generally falls below pretreatment levels. The initial rise in $PaCO_2$ with a fall in arterial pH, is usually observed during the first night after starting oxygen therapy, and is associated with increasing drowsiness, dullness, confusion and apathy. Thereafter, there is a gradual fall in the $PaCO_2$ to pretreatment or even lower levels and a return of pH toward normal, occurring pari passu with clinical improvement.
3. Relief of hypoxemia, but a rapid, progressive, marked increase in the $PaCO_2$ with an increasing respiratory acidosis (pH <7.25). This response is to be expected if oxygen is administered in an uncontrolled manner, using high oxygen concentrations. It can however also occur with carefully controlled and supervised oxygen therapy (O_2 concentration between 24% and 28%). The severe respiratory acidosis and the marked rise in the $PaCO_2$ can prove lethal in these patients.

Unfortunately, it is generally the severely hypoxic patient with a fairly high $PaCO_2$ to start with, who is more prone to developing a progressively increasing, dangerously high $PaCO_2$ with a dangerously low arterial pH (<7.2).

Box 7: Blood gas patterns observed in acute exacerbation of COPD

- Hypoxia + hypercapnia during crisis; hypercapnia persists after recovery from acute exacerbation
- Hypoxia + hypercapnia during crisis; normocapnia after recovery
- Hypoxia but no hypercapnia during crisis

It is important to understand why uncontrolled oxygen therapy (and in some patients even controlled oxygen therapy) can lead to a sharp rise in $PaCO_2$. It used to be believed that the essential drive to breathe in these patients was due to the prevailing hypoxia, because the respiratory center was considered to be relatively insensitive (compared to normal subjects) to the rise in $PaCO_2$. Giving a high FiO_2 (uncontrolled oxygen) would remove the hypoxic stimulus to breathe, so that the patient would have a further rise in $PaCO_2$. This is not true; the ventilatory drive in these patients is even more than normal. Uncontrolled O_2 therapy produces vasodilatation in the pulmonary capillaries due to relief of hypoxia. This leads to a further ventilation/perfusion (V/Q) mismatch with low ventilation-perfusion ratios. It is the increasing alveolar hypoventilation due to the above cause that leads to a sharp rise in $PaCO_2$. The blood gas patterns observed in acute exacerbation of COPD are listed in Box 7.

Patients who on conservative management (outlined earlier), and on controlled oxygen therapy show poor relief in hypoxia or show a progressive rise in the $PaCO_2$ with a fall in the arterial pH less than 7.25, require mechanical ventilator support. Ventilator support could be of two types: (1) noninvasive and (2) invasive. It should be noted that many patients with severe Grade IV COPD have a persistent hypercapnia between 50 mm Hg and 60 mm Hg even in a stable state. It is unwise to attempt to reduce a very high $PaCO_2$ seen during an acute exacerbation to normal levels. These patients tolerate a $PaCO_2$ between 50 mm Hg and 60 mm Hg fairly well.

Noninvasive Mechanical Ventilation[2,11,12]

Noninvasive positive pressure ventilation (NIPPV) has been proven to be useful in several studies of acute respiratory failure caused by an acute exacerbation of COPD. Studies show that the use of NIPPV is associated with a lesser risk of nosocomial infections, less antibiotic use, and a lower mortality when compared to patients who are equally ill but did not receive NIPPV.

NIPPV has the ability to increase alveolar ventilation, rest muscles of respiration, reduce work of breathing and prevent respiratory muscle fatigue. Potential benefits include an increase in tidal volume, a fall in respiratory rate, improved oxygenation, a fall in $PaCO_2$ and greater patient comfort.

Box 8: Indications and contraindications for NIPPV

- Indications for NIPPV—
  - Respiratory rate >30/min
  - Respiratory distress due to moderate or severe dyspnea
  - pH ≤7.30 and or a $PaCO_2$ >60 mm Hg, provided these values fail to improve or worsen after a trial of 6–12 hours of conservative treatment
- Contraindications to NIPPV—
  - Obtunded patient
  - Breathes very poorly, irregularly
  - Unable to protect the airway
  - Copious respiratory secretions
  - Risk of gastric aspiration
  - Hypotension; CVS instability
  - pH ≤7.20 with an acute rise of $PaCO_2$ >70 mm Hg

Abbreviations: NIPPV, noninvasive positive pressure ventilation; $PaCO_2$, arterial carbon dioxide tension; CVS, cardiovascular system.

When these benefits occur, they do so within a few hours of initiating NIPPV. Perhaps the most important advantage of NIPPV in an acute crisis of COPD is that it obviates the need for endotracheal intubation and invasive mechanical ventilation, which is far more inconvenient to the patient, and has more risks—particularly the risk of nosocomial infection.

Having said this, it is our considered opinion that many patients admitted to intensive care units in this country for an acute exacerbation of COPD are offered NIPPV when ventilatory support is not required, i.e. these patients would have recovered on conservative measures outlined above. Also, many such patients are offered NIPPV when they in fact needed prompt intubation and invasive ventilator support.

The indications for initiating NIPPV in an acute crisis of COPD are—

- Respiratory rate greater than 30/minute.
- Respiratory distress due to moderate or severe dyspnea.
- pH less than or equal to 7.30 and/or a $PaCO_2$ greater than 60 mm Hg, provided these values fail to improve or worsen after a trial of 6–8 hours (or even earlier) of conservative measures.

Noninvasive mechanical ventilation should not be used as the mode of ventilatory support if the patient is hemodynamically unstable, breathes poorly or irregularly, is unable to protect the airway, has copious respiratory secretions, and has a risk of aspirating gastric contents. It is preferable to intubate and ventilate those whose PaO_2 is less than 45 mm Hg and who are admitted with a pH less than 7.20. Patients who show an acute rise of $PaCO_2$ greater than 70 mm Hg are often obtunded, and in our opinion, are more effectively managed by endotracheal intubation and invasive ventilator support. Endotracheal intubation and ventilation should obviously be also resorted to when NIPPV fails to prove of benefit within 6–10 hours of its initiation, or even earlier, if the patient worsens on this mode of support. Indications and contraindications for NIPPV are listed in the Box 8.

Box 9: Indications for endotracheal intubation and ventilator support

- Respiratory rate >40/min
- Respiratory muscle fatigue
- Mental obtundation
- A silent chest—respiratory arrest
- Hypotension
- Falling pH <7.25
- PaO_2 <50 mm Hg
- Rising $PaCO_2$ >70 mm Hg, often ≥100 mm Hg

Implementation of NIPPV

Noninvasive positive pressure ventilation can be offered through either a light-fitting face mask or a nasal mask. Each has its own advantages. We prefer the face mask in patients with severe respiratory failure. A wide variety of ventilatory modes can be used in NIPPV. The biphasic positive airway pressure (BiPAP) mode allows for good gas exchange and effectively reduces both the work of breathing and patient distress. Pressure support ventilation (PSV) is perhaps an equally useful mode and is generally better tolerated than the assist-control mode. In a BiPAP mode, to start with, the inspiratory pressure (IP) is kept at 8–10 cm above the end-expiratory pressure (EP), so that if the EP is 5–7 cm H_2O, the IP is 12–15 cm H_2O. The pressure can then be adjusted to allow for effective alveolar ventilation and good gas exchange.

If the PSV mode is used for NIPPV, the IP support to start with is kept on 15–20 cm H_2O. A small PEEP of 4–5 cm H_2O may be of help in patients who have a large auto-PEEP, as it helps reduce inspiratory effort to generate inspiratory airflow in these patients.

Weaning from NIPPV is accomplished by progressively decreasing the level of IP support if the PSV mode is used, or by allowing the patient to be intermittently off NIPPV for increasing lengths of time.

Intubation and Mechanical Ventilation[2]

Patients who show a sharp progressive rise in the $PaCO_2$ with a pH less than 7.2 on controlled oxygen therapy, or those whose dangerous hypoxia stands unrelieved on conservative therapy or NIPPV, are best intubated and put on mechanical ventilator support. The indications for endotracheal intubation and ventilator support are listed in Box 9. Selection of cases for this mode of treatment is difficult. It would be disastrous for a patient and his family if after starting mechanical ventilation, it becomes impossible to wean the patient off ventilator support. In our opinion, the best indication whether to opt for invasive ventilator support or not, is the activity and state of health of the patient under basal conditions. If the patient's activity was hopelessly poor under basal conditions to start with (i.e. he was more or less confined to his bed due to poor respiratory reserve), it is unwise to opt for invasive ventilator support, and the family should be advised accordingly. If he was reasonably

Table 1: Principles of mechanical ventilation in patients with COPD with acute respiratory crisis

Ventilator settings	*Objectives*
Low tidal volumes of 350 mL (6–7 mL/kg) MV <5–6 L/min	• Prevents overinflation • Prevents dynamic hyperinflation and progressive increase in auto-PEEP
Rate: 12–14/min	• Decreases peak inflation pressure • Reduces risk of barotrauma
Flow rate 40–60 L/min	
I:E ratio of 1:3	• Allows good distribution of inspired gas, allows time for expiration
FiO_2 of 50–70%	• Allows quick correction of hypoxia
Sedate or use pancuronium	• Allows machine to take over, and prevents clashing with the machine

Note: (1) Lower $PaCO_2$ very gradually over 24 hours or even longer to 50 mm Hg—a PaO_2 of 60 mm Hg suffices. (2) If weaning is difficult, use pressure support ventilation.
Abbreviations: COPD, chronic obstructive pulmonary disease; PEEP, positive end-expiratory pressure; I:E ratio, inspiratory:expiratory ratio; MV, minute ventilation; $PaCO_2$, arterial carbon dioxide tension.

active prior to the crisis that brought him to the ICU, he should be offered ventilator support.

Endotracheal intubation in patients showing poor response to antibiotics, bronchodilators, physiotherapy and controlled oxygen therapy, offers two advantages: (1) it allows proper access for suctioning of respiratory secretions and (2) it allows mechanical ventilator support.

Mechanical ventilation is difficult in patients with chronic airways obstruction. We prefer and recommend the assist-control mode in patients with severe ARF, so that total support and appropriate choice of ventilator settings can be provided. Sedation and rarely, neuromuscular paralysis may be necessary for effective respiratory support. As recovery proceeds, or in patients who are not very ill, PSV may be used. The principles for successful ventilation are outlined above (Table 1).

- Small tidal volumes of 300–400 mL are used with minute ventilation not exceeding 5–6 L/minute. Lung protection measures require that peak pressures are not unduly high and that the plateau pressure does not exceed 30 cm H_2O. The FiO_2 is increased to 50–60% so that dangerous hypoxia is quickly corrected. It is unnecessary to aim for an oxygen saturation greater than 90%. The low tidal volumes prevent dynamic hyperinflation, thereby preventing a further increase in auto-PEEP, which is invariably present in these patients (see Section Pathophysiology). Low tidal volumes also lead to lower peak inflation pressures. This is a great advantage, as high peak pressures, if transmitted to the intrapleural space, cause a sharp reduction in the venous return and the cardiac output, and can produce sudden severe hypotension. In fact, hypotension should be carefully looked out for, particularly after starting ventilation. A fall in the arterial pressure should prompt one to further reduce the inflation pressure by further reducing the tidal volume. The blood pressure should also be raised by volume expansion or by using inotropic support. Once the patient is on mechanical ventilation with the hypoxia corrected by a high FiO_2, an increase in $PaCO_2$ need not be feared. Under these circumstances, death usually does not occur due to a high $PaCO_2$.

Sensitivity

The optimal triggering threshold is difficult in an acute COPD crisis in the presence of dynamic hyperinflation (i.e. auto-PEEP). This is because the patient has to generate a negative pressure at least equal to the level of auto-PEEP before interfacing with the preset sensitivity on the ventilator. If the auto-PEEP is high, the required inspiratory effort (before reaching trigger sensitivity) to initiate airflow is significant and this can lead to patient-ventilator dyssynchrony. Yet, if the trigger sensitivity is kept very low, the ventilator could be triggered very frequently and inappropriately. If the auto-PEEP is significantly raised, extrinsic PEEP is applied at a level well below the level of the auto-PEEP. This helps to reduce the effort needed to initiate inspiratory flow.

Ventilator requirements are so adjusted so as to bring down the raised $PaCO_2$ level very slowly over 24–48 hours. It is generally unnecessary to reduce the $PaCO_2$ to less than 50 mm Hg unless the basal $PaCO_2$ levels were normal. A sudden drop in the $PaCO_2$ is dangerous as it causes a sudden shift from respiratory acidemia to metabolic alkalosis and alkalemia. This can precipitate dangerous arrhythmias and cause sudden death.

- The flow rates used in such patients are usually between 40 L/minute and 60 L/minute, and the inspiration:expiration ratio is initially set at 1:3.
- Patients should not be allowed to clash with the machine; they can be given a neuromuscular relaxant, or sedated once they are put on ventilator support. Paralytic agents should if possible be avoided or used sparingly. The combined use of corticosteroids and muscle relaxants often causes a neuropathy or a neuromyopathy, characterized by extreme weakness of the extremities. The respiratory muscles may also be involved causing difficulties in weaning.
- Mechanical ventilator support is generally necessary for a period of 3–7 days. The maximum period over which we have used ventilator support, and then finally succeeded in weaning the patient, has been 6 weeks. An elective tracheostomy is preferred if ventilator support needs to be extended for more than 7 days, or if the patient has thick copious secretions which cannot be easily suctioned through the endotracheal tube.
- Weaning is generally carried out by the traditional methods. We have used intermittent mandatory ventilation, and

Box 10: Complications during acute respiratory failure in COPD

- Pulmonary infection
- Fluid, electrolyte and acid-base disturbances
- Respiratory acidosis with hypokalemic metabolic alkalosis
- Severe water logging can occur due to salt and water retention
- Cardiac arrhythmias
- Right-sided heart failure
- Hypotension if there is marked auto-PEEP
- Pneumothorax
- Complications due to mechanical ventilation
- Gastrointestinal bleeds
- Neuromyopathy caused by steroids, steroids and muscle relaxants or due to prolonged critical care (critical care neuromyopathy)
- Pulmonary thromboembolism
- Mental depression

Abbreviations: COPD, chronic obstructive pulmonary disease; PEEP, positive end-expiratory pressure.

PSV, but have never been totally convinced of their absolute necessity. The patient is taken off ventilator support when he can maintain an adequate gas exchange on his own. This generally happens when infection has been controlled, airways obstruction has decreased, and V/Q abnormalities have been significantly rectified.

Older patients with IHD often need careful cardiovascular support. The presence of associated LV failure with pulmonary edema, together with generalized water retention is not uncommon in these patients. It is indeed remarkable how good ventilator support with improvement in blood gases initiates a diuresis in these patients, even though earlier use of large doses of furosemide might have been ineffective. Correction of severe hypoxia and hypercapnia are probably responsible for the improved cardiac-cum-renal function and diuresis.

- ❑ Expert nursing, humidification of inspired oxygen and persistence with the regime outlined earlier, are all essentials of good respiratory care in these patients.

Treatment of Right Heart Failure

Patients suffering a severe exacerbation of COPD often go into right heart failure with edema of the feet and legs and with distended jugular vein. Intravenous furosemide is useful; digoxin is however of not much use and may well trigger arrhythmias. At times the edema is massive and appears unresponsive to diuretics. This is particularly observed in patients who are severely hypercapnic. Ventilator support which lowers the $PaCO_2$ to less than or equal to 50 mm Hg is invariably associated with significant diuresis, the patient becoming edema free within a few days. Patients in right heart failure should always be given prophylactic anticoagulant therapy, preferably with low molecules weight heparin.

Box 11: Management of acute respiratory crisis in patients with COPD

- Improve ventilation, correct ventilation-perfusion mismatch, relieve severe hypoxia and correct low pH—
  - Controlled oxygen therapy (24–30% oxygen)
  - Treat infection with antibiotics
- Relieve airways obstruction—nebulize with duolin 6–8 hourly, ipratropium bromide 12 hourly—
  - Use of corticosteroids—IV or orally; nebulize with 1 mg budesonide 12 hourly
  - Theophylline
- Physiotherapy to help drain copious secretions and prevent sputum retention
- Ventilator support when so indicated
- Cardiovascular support when necessary
- Treat complications encountered during acute respiratory failure—
  - Correct fluid and electrolyte disturbances
- Management of cardiac complications, e.g. arrhythmias, hypotension, right-sided heart failure and pulmonary thromboembolism—
  - Treat GI bleeds
  - Drain even a shallow pneumothorax

Abbreviations: COPD, chronic obstructive pulmonary disease; GI, gastrointestinal.

TREATMENT OF COMPLICATIONS DURING ACUTE RESPIRATORY FAILURE IN EXACERBATION OF COPD

A number of complications may arise in critically ill patients with ARF resulting from an acute exacerbation of COPD. These are listed in Box 10. These should be promptly diagnosed and treated. The most dangerous complications outside the respiratory system are cardiac arrhythmias and hemodynamic instability.

Cardiac Arrhythmias

Cardiac arrhythmias are frequently observed in these patients. Supraventricular tachycardia, multifocal atrial tachycardia and atrial fibrillation are common; atrioventricular (AV) dissociation and multiple ventricular extrasystoles may also occur. The mortality rate is significantly higher in patients having arrhythmias.

Hemodynamic Instability

Patients with COPD often suffer from pulmonary hypertension. An acute exacerbation of COPD worsens pulmonary hypertension due to hypoxic vasoconstriction, dynamic hyperinflation, or the presence of auto-PEEP during mechanical ventilation. A sharp increase in pulmonary artery pressure leads to severe right ventricular dysfunction, right-sided heart failure, with a fall in both systolic and mean arterial blood pressure. An IV fluid challenge expands the intravascular

pulmonary bed and improves right ventricular pump function. It should be the initial step in the management of hypotension and hemodynamic instability in an acute crisis of COPD. If the hemodynamic state fails to improve, inotropic and/or vasopressor support is necessary. Ventilator adjustments to reduce dynamic hyperinflation and auto-PEEP are also necessary.

The management of acute exacerbation of COPD is outlined in the Box 11.

PROGNOSIS

The prognosis for patients treated in the ICU is unsatisfactory, particularly so if the patients have received invasive ventilatory support. The mortality rate in the above patients is as high as 25% with a 1 year mortality quoted at 39%.[13,14]

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CHAPTER 32

Acute Lung Injury and Acute Respiratory Distress Syndrome

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GENERAL CONSIDERATIONS

The acute respiratory distress syndrome (ARDS) is an important condition characterized by noncardiogenic increased permeability, inflammatory pulmonary edema, with diffuse alveolar damage; it leads to hypoxemic respiratory failure necessitating ventilator support and prolonged intensive care.

The first description of what probably was ARDS was given by Osler in his Textbook of Medicine in 1927. He wrote of uncontrolled septicemia leading to pulmonary edema and went on to describe the clinical features and autopsy findings very nearly as we know them today. In 1967, Ashbaugh, Bigelow and Petty[1] reported in the Lancet the occurrence of noncardiogenic pulmonary edema and acute respiratory failure in a number of diverse pathologies not directly involving the lungs. They termed this condition the adult respiratory distress syndrome. Semantically speaking, this was an unfortunate term. The syndrome can occur at all ages and is not related in its pathogenesis and pathology to the respiratory distress syndrome of the newborn. Also, the connotation of respiratory distress is both vague and common to numerous other unrelated pathologies in cardiorespiratory medicine. The syndrome is now termed the acute respiratory distress syndrome (ARDS). Semantic confusion would have been avoided if from the very outset the condition had been termed acute lung injury (ALI) which could then have been graded as mild, modarate or severe. Since 1967, the syndrome has been reported from many countries, including India.[2] The precipitating factors have been recognized and the pathology of the lung has been elucidated. However, the pathogenesis after more than 40 years of research remains unclear and the mortality in spite of expert intensive care, even today is as high as 30–60%.

EPIDEMIOLOGY

The incidence of ARDS even in Western countries has not been clearly established. The National Heart, Lung and Blood Institute sponsored ARDS Network of 20 hospitals estimated that the incidence could be as high as 64 cases per 100,000 population. The prevalence in developing countries including India is unknown. ARDS constituted a little over 4% of intensive care unit (ICU) admissions in our unit over a 5-year period. It is unquestionably a problem that is likely to be encountered with increasing frequency by all physicians who look after critically ill patients.

DEFINITION AND CONCEPT

ARDS is characterized by (1) an antecedent history of a precipitating condition; (2) respiratory distress and refractory hypoxemia not responding satisfactorily to supplemental oxygen and invariably necessitating the use of mechanical ventilatory support; (3) radiographic evidence of newly evolving bilateral pulmonary infiltrates and (4) pulmonary artery occlusion pressure (PAOP) less than 18 mm Hg in the presence of a normal colloid oncotic pressure.

The physiological changes underlying the above clinical definition include a reduced functional residual capacity (FRC), stiff lungs (reduced pulmonary compliance), increased ventilation-perfusion inequalities, an increase in the right to left shunt within the lungs and an increase in the extravascular water content of the lungs with, as already mentioned, a normal PAOP. *The underlying pathological abnormality is damage to the alveolar capillary membrane with increased capillary permeability, leading to edema, inflammation and subsequent fibrosis.*

Table 1: The American-European Consensus Definition of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

ALI	*ARDS*
Acute onset respiratory failure	Acute onset respiratory failure
Bilateral chest infiltrates on frontal radiographs	Bilateral chest infiltrates on frontal radiographs
PaO_2/FiO_2 <300	PaO_2/FiO_2 <200
Absence of elevated left heart filling pressure (PAOP <18 mm Hg)	Absence of elevated left heart filling pressure (PAOP <18 mm Hg)

Abbreviations: PaO_2, arterial blood gas oxygen tension; FiO_2, fraction of inspired oxygen; PAOP, pulmonary artery occlusion pressure.

The American-European Consensus Conference in 1994[3] clinically defined and distinguished between ALI and ARDS, so as to avoid semantic confusion. The American-European Consensus Definition of ALI and ARDS is given in Table 1.

A more recent definition has been proposed through a Delphi method. This definition again primarily relies on hypoxemia [arterial blood gas oxygen tension (PaO_2)/fraction of inspired oxygen (FiO_2) <200, with a positive end-expiratory pressure (PEEP) >10 cm H_2O], and the presence of bilateral chest infiltrates as detected on chest radiography. All definitions exclude the presence of unilateral lung injury and the presence of cardiogenic pulmonary edema detected either through clinical judgment or through measurement of PAOP.

Till very recently the most widely accepted definition of ARDS was that proposed by the American-European Consensus Committee (AECC) in 1994. However, the reliability and validity of this definition has been recently questioned. In 2011, a panel of experts (initiated by the European Society of Intensive Care, and endorsed by the American Thoracic Society) developed the Berlin Definition.[4] A draft definition proposed three mutually exclusive categories of ARDS based on degree of hypoxemia—

1. Mild (PaO_2/FiO_2 <300 mm Hg).
2. Moderate (PaO_2/FiO_2 <200 mm Hg).
3. Severe (PaO_2/FiO_2 <100 mm Hg).

Four ancillary variables for severe ARDS were considered: (1) radiographic severity, (2) lung compliance (40 mL/cm H_2O), (3) PEEP (>10 cm H_2O) and (4) corrected expired volume/minute (10 L/minute). The draft definition was empirically evaluated using patient-level meta-analysis of 4,188 patients with ARDS from four multicenter clinical data sets and 269 patients with ARDS from three single-center data sets. It was observed that the four ancillary variables did not contribute to the predictive validity of severe ARDS for mortality and were removed from the definition.

The three mutually exclusive stages of categories of ARDS as proposed by the Berlin Definition: (1) mild, (2) moderate and (3) severe ARDS were shown to be associated with increasing mortality.

- Mortality in mild [27%; 95% confidence interval (CI), 24–30%].
- Mortality in moderate (32%, 95% CI, 29–34%).
- Mortality in severe (45%; 95% CI, 42–48%).

Median ventilator free days declined with the severity of ARDS.

Compared to the AECC definition, the final Berlin Definition had better predictive validity for mortality.

Unquestionably, there is a definite advantage to an internationally accepted Definition, whether it be the AECC definition or the Berlin Definition. However, all definitions of ARDS have lacunae and limitations. These need to be considered for a balanced perspective of the syndrome.

- The present definition does not include any etiology or responsible risk factors. Perhaps this is because there are many (and a growing number of) background risk factors—some common and others uncommon. Also there may be more than one responsible factor in a patient.
- Though ARDS signifies noncardiogenic pulmonary edema, patients with a background of left ventricular dysfunction and raised left atrial pressure may fortuitously suffer from a risk factor such as sepsis which could further evolve into ARDS. Both ARDS and cardiogenic pulmonary edema may thus coexist. This is uncommon, but has been observed in our ICU. Again, in the natural history of ARDS due to severe sepsis, cardiac function is often seriously compromised with a sharply reduced ejection fraction and raised filling pressures. When a patient is seen for the first time at this juncture, diagnosis is difficult.
- Bilateral chest infiltrates have been taken as a surrogate marker for the increased permeability inflammatory pulmonary edema that characterizes ARDS. Meade and colleagues[5] have shown that the specificity of chest radiographs in indicating inflammatory edema is questionable. Similar infiltrates on a chest radiography can occur with atelectasis, consolidation, interstitial and intra-acinar edema
- The concept of ARDS as stated by the American-European Congress Conference is narrow in its perspective. An expanded concept should include not only the severity of the ALI, but also the background factor causing or precipitating the syndrome, and most importantly the associated or evolving dysfunction of organ systems. *Most investigators consider ALI/ARDS as merely one facet of the multiple organ dysfunction syndrome.*
- The diagnostic accuracy of the different definitions of ARDS has been recently assessed using as a reference or gold standard the finding of diffuse alveolar damage at autopsy. The commonly accepted criteria for the diagnosis of ARDS as stated by the American-European Congress Conference showed an acceptable sensitivity (0.83%) but a poor specificity (0.51%).

We therefore feel that the correct definition of ARDS is still an unsettled issue. Randomized trials using different ventilatory

and other strategies to test for improved survival have been based on enrolling patients according to a given definition. It is obvious that an inappropriate definition of ARDS would lead to inappropriate enrollment of patients in trials, which in turn could lead to biased and misleading results.

ETIOLOGY

A variety of clinical disorders and risk factors can lead to ALI and ARDS. The incidence of various risk factors in relation to ARDS will depend on the geographical areas and the population that is studied. In India and in other tropical developing countries in addition to the risk factors observed in the West, there are special important risk factors chiefly confined to tropical poor countries.

The various clinical disorders that can lead to ALI or ARDS may do so by directly involving the lung (direct injury), or may involve the lung indirectly (indirect injury). Our experience on ARDS with regard to etiology and mortality in relation to each etiological factor is summarized in Table 2.

In 243 patients of ARDS studied over several years in our ICU, direct injury was the etiological factor in 82 patients; indirect injury was the causative factor in 105 patients; 56 patients developed ARDS due to fulminant infections and problems peculiar to the tropical and developing countries of the world—for convenience these 56 patients were categorized under ARDS due to tropical problems. The first two groups of patients for convenience were categorized under nontropical problems, i.e. problems more or less common to the whole world. Though the exact incidence of various clinical disorders causing ALI/ARDS in different critical care units in India may vary for several reasons, the nature of risk factors is by and large common to critical care units in the large metropolitan centers of the country.

The most important cause of direct injury perhaps all over the world is acute pulmonary infection (chiefly bacterial or viral pneumonia).[6] Aspiration pneumonia is also an important risk factor, both aspirated gastric acid and enzymes contributing to lung injury. After aspiration, lung injury may take some hours to evolve and manifest. Direct trauma to the chest with contusions within the lung is an important cause particularly in trauma units. Polytrauma even when not directly involving the chest is an even more important cause and is probably due to inflammatory mediators released from trauma sites acting on the lungs.

Sepsis is unquestionably the most important cause of ALI/ARDS all over the world.[7] In sepsis, ALI and ARDS form merely one facet of the multiorgan dysfunction syndrome. The incidence of ALI and ARDS in severe sepsis or septic shock is over 25%. Sepsis not only initiates ALI but also perpetuates it. Even when ARDS is caused by a direct injury or insult to the lung, sepsis may subsequently supervene as a major complication and can worsen lung injury and cause multiple organ dysfunction. When sepsis is the indirect cause of ALI, the source of sepsis is most frequently intra-abdominal. On the other hand, when sepsis is a supervening complication in a patient suffering from ALI due to any other etiology, the source of sepsis is most frequently within the lung itself (Fig. 1).

Acute pancreatitis, burns and poisoning (in particular organophosphorus poisoning) are other important causes of ARDS.

Table 2: The etiology of acute respiratory distress syndrome (ARDS) as observed in our unit with observed mortality for each etiological factor. Note the difference in mortality between ARDS and multiple organ dysfunction syndrome (MODS) in tropical problems and nontropical problems

	Total	*Expired*	*Mortality (%)*
Total number of patients	243	128	53
Patients with tropical problems	56	15	27
Patient with nontropical problems	187	113	60
Patients with tropical problems (N = 56)	*Total*	*Expired*	*Mortality (%)*
Tetanus	9	4	44
Organophosphorus (OP) poisoning	10	1	10
Cerebral malaria	13	4	31
Gram-negative septicemia from contamination food	5	0	0
Miliary/Disseminated hematogenous tuberculosis (TB)	9	3	33
Amebiasis	5	2	40
Salmonella infections	3	0	0
Rabies	1	1	100
Leptospirosis	1	0	0
Total	56	15	27
Patients with nontropical problems (N = 187)			
Direct injury:	*Total*	*Expired*	*Mortality (%)*
Acute pulmonary infection	46	32	70
Aspiration pneumonia	20	13	65
Direct trauma	7	2	29
Noxious fumes	5	0	0
Pulmonary vasculitis	4	0	0
Total	82	47	57
Indirect injury:	*Total*	*Expired*	*Mortality (%)*
Severe sepsis	68	47	69
Pancreatitis	9	5	56
Burns	4	3	75
Extrathoracic injury	5	1	20
Poisoning	2	0	0
Miscellaneous	17	10	59
Total	105	66	63

Fig. 1: Acute lung injury in a patient who developed peritonitis following a cesarean section

There are a number of varying miscellaneous causes being reported with increasing frequency from different parts of the world. Among these, multiple blood transfusions head the list.[8] ARDS following multiple blood transfusion has been reported in both trauma patients as also in nontrauma patients such as patients transfused following massive gastrointestinal bleeds. In trauma patients, systemic inflammatory mediators may perhaps play a greater or equal role as multiple blood transfusion in causing ALI/ARDS. Current evidence suggests that the risk of lung injury increases with the duration of stored blood.

Transfusion-related acute lung injury (TRALI) resembles ALI/ARDS, yet is not the same.[9] This form of injury can be caused by transfusion of even small quantities of whole blood or any blood product. The cause is believed to be due to passively transfused antibodies that act as leukagglutins attaching to antigens on the recipient leukocytes, thereby causing lung injury, TRALI manifests with breathlessness during or after transfusion of whole blood or a blood product accompanied by shadows in mid and lower zones of both lung fields. Tachycardia and a fall in oxygen saturation are often observed. TRALI is often mistaken for acute left ventricular failure.

Tropical Infections and Problems[10,11]

It is pertinent and important to briefly outline tropical problems causing ALI and ARDS. These, in our experience, include fulminant *Plasmodium falciparum* infections, severe tetanus, severe typhoid infection, severe dengue, fulminant Gram-negative infection following ingestion of contaminated food, acute miliary tuberculosis, acute disseminated hematogenous tuberculosis, fulminant amebic infections of the liver and large bowel, fulminant leptospirosis, melioidosis, hemorrhagic fevers and rabies. Severe organophosphorus poisoning is the most frequently encountered poisoning causing ARDS in Western India. In the north, aluminum phosphide (added generally for the preservation of food grains) poisoning is an important cause of severe ARDS which invariably ends fatally. Each of these tropical problems can lead not only to ARDS, but to progressive multiple organ failure and death.[12] The most important of these causes are fulminant *P. falciparum* infections, tetanus, fulminant dengue, acute leptospiral infection, fulminant *Bacillus typhosus* infection, acute miliary tuberculosis and acute hematogenous disseminated tuberculosis (Figs 2 to 8).

The following clinical forms of ALI/ARDS have been noted in relation to severe *P. falciparum* malaria—

- Acute pulmonary edema due to hyperpyrexia (temperature >107°F).
- Progressive bilateral shadowing within the lungs characterized physiologically by marked ventilation-perfusion inequalities, but by only a slight increase in the right to left shunt within the lungs—recovery is possible with good management.
- Progressive bilateral fluffy shadows characterized physiologically by a marked increase in the right to left shunt—prognosis of patients in this category is grim.
- Acute respiratory distress syndrome caused by disseminated intravascular coagulopathy complicating falciparum infection.
- Acute respiratory distress syndrome due to aspiration of gastric contents in obtunded patients.

The time from the original insult (direct or indirect) to the development of full-blown ALI has been studied in many large series. In Petty's original group, it ranged from 1 hour to 96 hours. In a comprehensive, recent epidemiological study, 80% of patients had developed ALI within 48 hours of the initial insult and 90% by 80 hours. This latent period offers a window of opportunity for therapeutic interventions, when effective blockers of the inflammatory process can be identified. Indeed, today there is a massive search for circulating markers of ALI which can be identified in the serum or bronchoalveolar lavage fluid.

PATHOLOGY

The work of Gattinoni and his colleagues on CT scans in ARDS[13] has brought forth important new concepts. The first of these concepts is that the lung in ARDS is not homogeneously affected. The most affected part of the lung is the most dependent portion. This dependent area is consolidated and represents core disease, generally constituting about 24% of lung weight. The part or zone above this dependent portion is collapsed lung, the collapse being due to the weight of inflammatory edema which is the hallmark of ARDS; still above the collapsed lung and the zone of inflammatory edema, is the zone of normally aerated or even overventilated

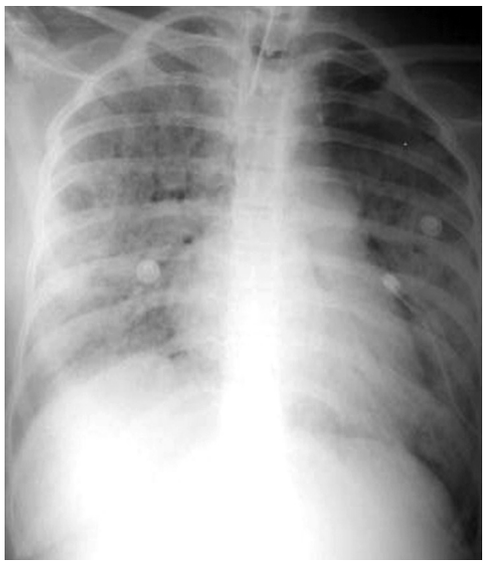


Fig. 2: Acute lung injury in a patient with acute disseminated hematogenous tuberculosis (TB). This patient presented with pyrexia of unknown origin, and rapidly deteriorated, developing ARDS and multiorgan failure. A fiberoptic bronchoalveolar lavage (BAL) was done and demonstrated the presence of acid-fast bacilli (AFB)

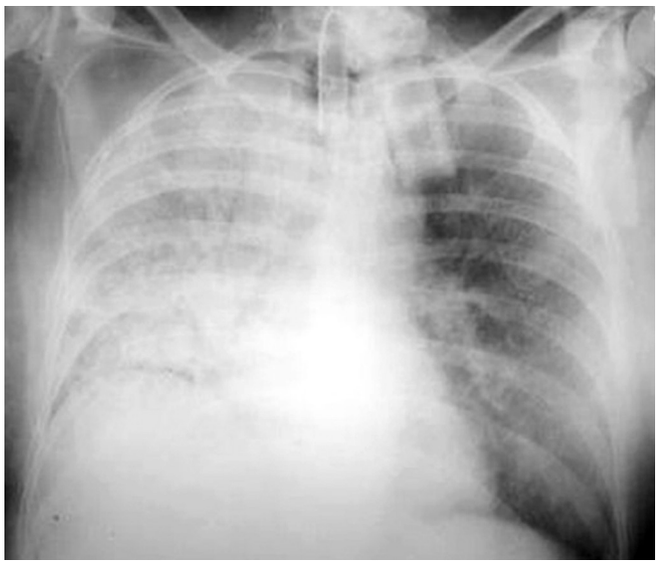


Fig. 3: Acute respiratory distress syndrome (ARDS) in a patient with fulminant *P. falciparum* infection, though both lungs are involved, one seems more involved than the other

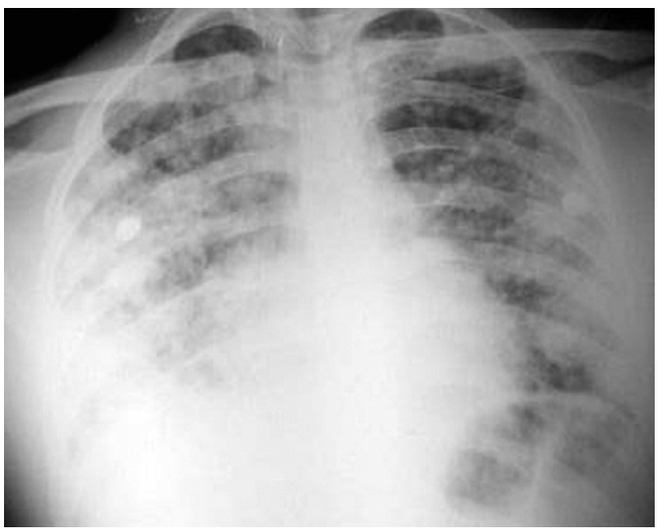


Fig. 4: ARDS in typhoid; note extensive bilateral shadowing

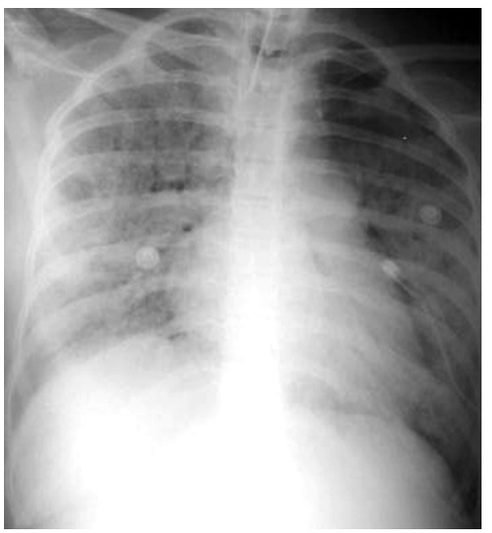


Fig. 5: ARDS in tetanus

lung. The extent of the zone constituting collapsed lung varies. Of importance is the fact that this collapsed lung is capable of being opened up, that is to say it is recruitable by ventilatory measures (raising inspiratory pressure from +5 cm to 45 cm H_2O). The greater the recruitability, the greater the inflammatory edema, the more severe the disease and worse the prognosis. The lesser the recruitability, the lesser the inflammatory edema; the disease is then milder and the prognosis better (Figs 9 and 10).

The above views put forth by Gattinoni not only allow a better conceptualization of ARDS, but also better prognostication, and perhaps most importantly may further guide ventilatory strategies in the management of this syndrome.

The basic pathological feature is damage to the alveolar capillary membrane leading to an increased permeability, inflammatory interstitial and alveolar edema, alveolar atelectasis, consolidation and diffuse alveolar damage. Three overlapping phases are observed—

1. Exudative phase in which there is an alveolar exudate with hyaline membrane formation along the alveolar ducts and within the alveoli.
2. Proliferative phase in which there is a proliferation of inflammatory cells, lymphocytes and type 2 pneumocytes. Organization of the inflammatory exudate combined with damage to the surfactant leads to obliteration of air spaces, atelectatic alveoli and a poorly compliant lung.

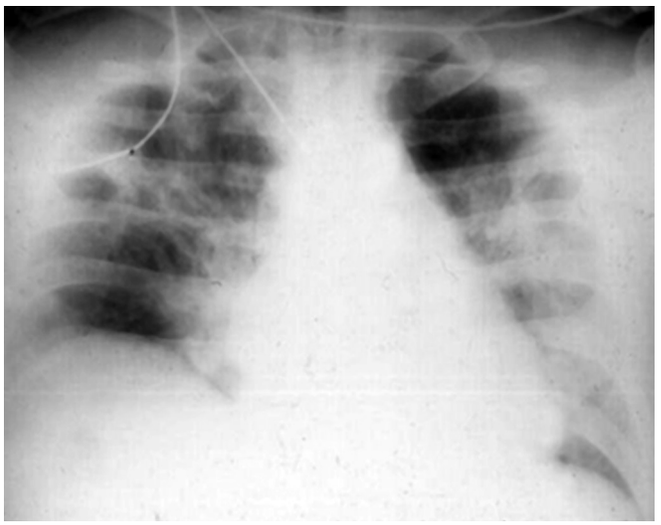


Fig. 6: ARDS in malaria, showing extensive bilateral fluffy shadows

Fig. 7: Acute respiratory distress syndrome (ARDS) in a patient with very severe tetanus

3. Fibrotic phase which follows soon upon the proliferative phase, and is characterized by fibroblasts laying down fibrous tissue that strangles alveoli, and further reduces pulmonary compliance.

Severe lung injury distorts the pulmonary vasculature.

Distortion with remodeling of the vasculature is due to fibrous tissue formation, thromboembolism and increased muscularization with thickening and intimal fibrosis of the larger arteries. Thrombi may be present in the microcirculation and in the larger vessels. They may form in situ, or may have an embolic source. The end-result is an obstructed, distorted pulmonary circulation with increased pulmonary vascular resistance, causing pulmonary hypertension.

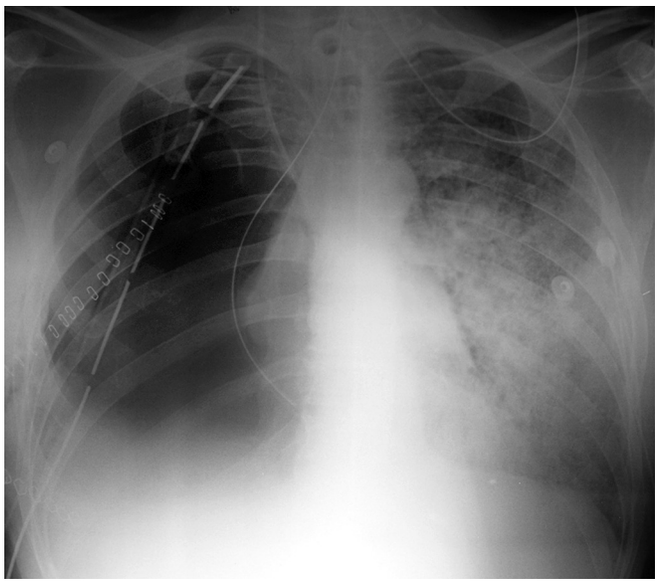


Fig. 8: Acute lung injury in a patient with acute disseminated hematogenous tuberculosis (TB). This patient presented with pyrexia of unknown origin, and rapidly deteriorated, developing ARDS and multiorgan failure. A fiberoptic bronchoalveolar lavage (BAL) was done and demonstrated the presence of acid-fast bacilli (AFB)

PATHOGENESIS

The pathogenesis of ALI continues to remain unclear. Even so, current research allows a better comprehension of what transpires in this syndrome at a cellular and molecular level. Research into molecular genetics has revealed a complex network of interacting factors at the cellular level. It is clear that the cascade of mediators is far more complex than we thought, and many of yesterday's putative mediators are in reality modulators and regulators that fine-tune the inflammatory cascade, rather than cause it. Flowchart 1 illustrates the basic steps in the pathogenesis of ALI and organ failure.

Role of Cytokines, Neutrophils and the Coagulation System[14]

Cytokines, which are cell-derived peptide compounds, are the main mediators. Recombinant cDNA technology has permitted identification of the existence, structure and function of several cytokines. The cytokine on which most attention is currently focused is the tumor necrosis factor (TNF). This cytokine has a molecular weight of 17 kD and is released from macrophages in response to Gram-negative bacterial endotoxin. TNF is one of the main mediators of the septic state. After injection of endotoxin into animals or humans, TNF can be detected in the serum, the levels peaking at 2 hours. When TNF is infused into the sheep model, ALI is produced. Three other cytokines of importance mediating inflammatory response include neutrophil-activating peptide (NAP), interleukin-6 (IL-6), IL-8 and macrophage inflammatory proteins 1 and 2 (MIP 1 and 2). The neutrophil plays a vital role in the inflammatory response, and TNF is the

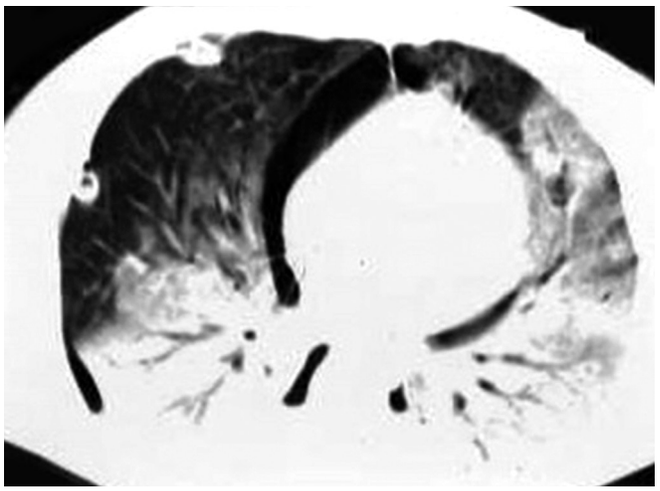


Fig. 9: High-resolution computed tomography (HRCT) of the chest in ARDS. The most dependent part of the lung is dense and consolidated; above this is a collapsed zone, the collapse being due to the weight of inflammatory edema; right on top is normally aerated lung

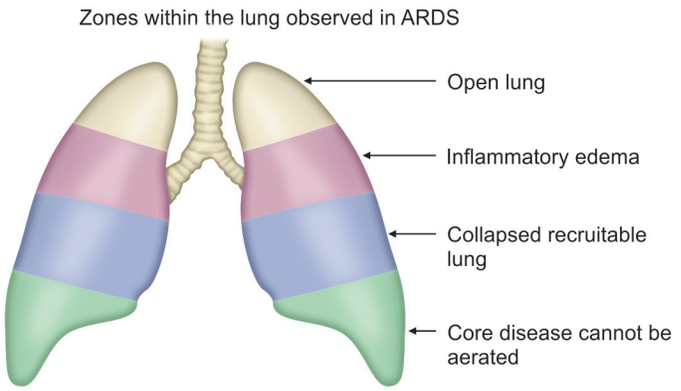
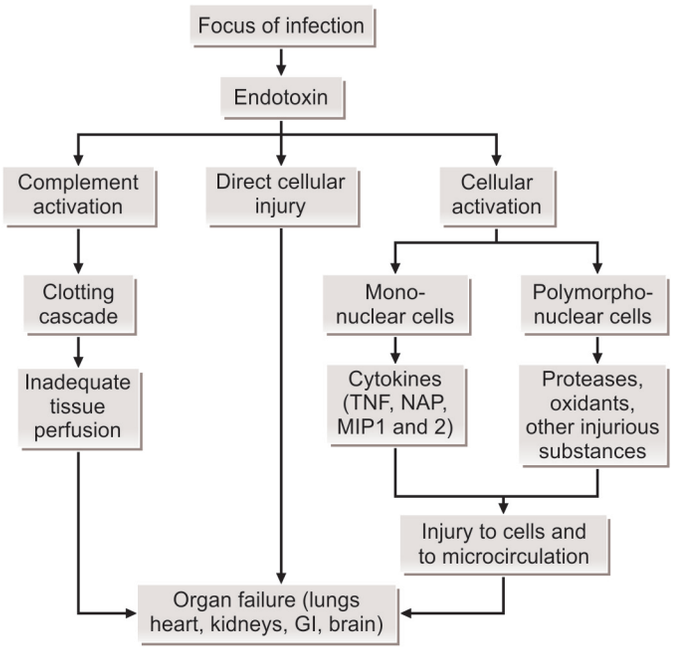


Fig. 10: A schematic representation of 'zones' within the lungs in ARDS. The most dependent zone is consolidated lung which cannot be aerated; above this is collapsed but recruitable lung; still above is the zone of inflammatory edema, the weight of which is responsible for the zone of collapsed recruitable lung; right at the top is normally ventilated or even hyperventilated lung

chief mediator that promotes adherence of the neutrophils to the vascular endothelium and together with IL-8 causes and enhances neutrophil activation. The primed neutrophils degranulate, releasing proteases, reactive oxygen species, leukotrienes, all harmful to lung structure and function. The lipid mediators and platelet-activating factor also enhance inflammation.

The activation of the coagulation and complement systems promotes coagulation and decreases fibrinolysis. Endothelial damage results in pulmonary edema with a disturbance in pulmonary microcirculation. The end result is increasing respiratory failure with an increasing poverty of gas exchange, often leading to death. As mentioned earlier, changes in the lung often form just one facet of similar changes in other organs of the body.

Flowchart 1: Pathogenesis of acute lung injury and organ failure in sepsis



Abbreviations: TNF, tumor necrosis factor; NAP, neutrophil-activating peptide; MIP, macrophage inflammatory protein; GI, gastrointestinal.

There is a complex, poorly understood interaction at the molecular and cellular level as the syndrome continues to evolve. This interaction and inter-relation will continue to be the subject of future research.

Unfortunately there is no definite biomarker which can reliably identify patients at risk, or assess the prognosis in ARDS. IL-6 and IL-8 can be found in alveolar fluid and in plasma but these are nonspecific markers of lung inflammation. The ARDS network trial[15] showed that high levels of IL-6 and IL-8 were associated with increased morbidity and mortality and that the strategy of using low tidal volumes attenuated the inflammatory response of the disease, suggesting that alveolar stretch is linked to and perhaps worsens the inflammatory response.

Alterations in Cardiopulmonary Physiology

The pulmonary edema, atelectasis, proliferation of inflammatory cells and increasing fibrosis occurring as a result of injury, produce a fall in the total lung capacity and FRC by 50%. The low lung recoil pressure at FRC leads to early closure of the small airways, with further alveolar collapse, necessitating high inflation pressures to expand or reinflate the lungs. The physiological consequences are an increase in the right to left shunt within the lungs due to perfusion of atelectatic alveoli, increased ventilation-perfusion inequalities, increase in dead space and increasingly noncompliant or stiff lungs. Injury as stressed earlier may be mild, moderate or severe. Of equal importance is the fact that even in severe injury, the lungs are not evenly or homogeneously affected. Computerized tomography (CT) as mentioned earlier has demonstrated a

three-zone model of the lung. This three-zone model of the lung in ARDS has already been discussed under Pathology.

Severe lung injury is sooner or later associated with increasing pulmonary hypertension. The latter is due to hypoxia and to an obstructed, distorted pulmonary circulation. The resultant increase in right ventricular afterload can not only lead to right heart failure, but also cause a shift of the septum to the left. The septal shift can significantly reduce left ventricular filling and stroke volume.

Myocardial dysfunction is an important feature of ALI. It is contributed to by a circulating myocardial depressant factor (probably the same as TNF) in patients with sepsis. A significant fall in cardiac output is frequently observed in these patients, particularly when the mean pulmonary artery pressure exceeds 35 mm Hg. A fall in cardiac output, particularly when combined with a low oxygen tension in arterial blood, can cause a significant reduction in oxygen transport or delivery (DO_2) to the tissues. A decreased DO_2 in association with a possible abnormality of oxygen uptake by the tissues, so frequently observed in ARDS, invariably spells disaster.

CLINICAL FEATURES

Against a background of one of the etiologies mentioned earlier, the patient with ARDS presents with rapidly worsening dyspnea and restlessness. On examination, such a patient has tachycardia, tachypnea and increasing hypoxemia despite supplemental oxygen. Auscultation reveals scattered crackles and occasionally a wheeze. The condition may evolve rapidly over a few hours, or may take a few days to reach its maximum intensity. Respiratory distress is obvious, and the accessory muscles of respiration are active. Cyanosis may occur, but is not always clinically evident in spite of severe hypoxemia.

In the early stages, a slight but disproportionate tachypnea may be the only warning sign of early ALI, and in an appropriate setting this must never be ignored, even in the absence of auscultatory crackles, and with a normal chest X-ray. An important warning diagnostic feature in the early phase is a slight fall in the PaO_2 and an increased alveolar-arterial oxygen gradient.

As the respiratory failure worsens, one or more other organ systems may show signs of dysfunction and failure. This is in keeping with the current concept that ALI is a multisystem disease, with the changes in the pulmonary endothelium mirroring widespread endothelial damage in other organs.

DIFFERENTIAL DIAGNOSIS

The lack of specificity in the radiological picture and in the diagnostic features proposed by the American-European Congress Conference have already been commented upon. The differential diagnosis includes—

- Other causes of air space consolidation—multiple pulmonary infarcts, multiple areas of atelectasis (as after major upper abdominal or cardiothoracic surgery), pneumonia, atypical pneumonia, Legionnaire's disease, alveolar hemorrhage, alveolar proteinosis, eosinophilic pneumonia and bronchiolitis obliterans with organizing pneumonia (BOOP).
- Acute exacerbation of previously unrecognized low-grade interstitial lung disease or acute interstitial pneumonia. The latter may be impossibly difficult to differentiate from ARDS without a lung biopsy.
- Cardiogenic pulmonary edema. Cardiac enlargement, the presence of more centralized edema, Kerley's lines, help in radiological differentiation. Clinical history and examination of the cardiovascular system are of critical importance. In difficult problems, a Swan-Ganz catheter may be used to determine PAOP. It is to be noted that in intra-abdominal pathologies, the rise in intra-abdominal pressure may cause a rise in the PAOP and mislead the clinician.

COMPLICATIONS

Death is uncommon from severe refractory hypoxia, provided the patient receives good ventilator support. In our unit, it occurs in not more than 10% of patients.

Nosocomial Pneumonia[16]

This is an extremely important complication. The incidence of this complication in severe ALI (ARDS) varies in different units, and in our ICU is about 15%. The incidence increases with the length of time on ventilator support, and is most marked when ALI is due to severe abdominal sepsis. It is less than 5% when ALI is caused by a direct insult, e.g. inhalation of noxious fumes, near-drowning, chest trauma, even when ventilator support is prolonged for weeks.

The lung injury per se, together with improper ventilatory management (such as use of high inflation pressures, high V_{Ts}, high FiO_2), and the prolonged use of PEEP, also probably impair local immune and other defense mechanisms within the lung, and predispose to iatrogenic infection and sepsis. Background illnesses which impair immune function and malnutrition either present before the ALI or occurring during the evolution of the syndrome are other important predisposing factors. Colonization of the upper respiratory tract and of the GI tract by Gram-negative organisms remains an important source of infection.

The diagnosis of nosocomial pneumonia is difficult in the presence of shadows caused by atelectasis and edema. We have missed a good-sized lung abscess causing an empyema in a patient with ARDS due to severe tetanus, the diagnosis being apparent only at autopsy. Suspicion of a nosocomial infection should prompt a CT of the chest which may reveal an abscess or an empyema undetected on an X-ray. The choice of antibiotics in the management of nosocomial pneumonia is empiric, and will depend on the nature of bacteria causing nosocomial pneumonia and their sensitivity to antibiotics in a critical care unit.

Multiple Organ Dysfunction[17]

The better and more intensive the care offered to the patient, and hence the longer he is kept alive, the more often is the complication of multiple organ dysfunction observed. It occurs early and most frequently when sepsis is the cause of ALI. It can however complicate the course of ALI from any cause.

In our experience, renal dysfunction occurs in 30–40% of patients, cardiovascular dysfunction necessitating inotropic support in 50–70% of patients, and liver cell dysfunction occurs in about 50% of patients. Complications and dysfunction involving the GI tract are observed in 20–30% of patients. There is an obvious inter-relation between various organ systems, so that impairment of one organ system induces, amplifies and modulates impairment in other organ systems.

Translocation of bacteria from the lumen of the gut to the lymphatics, peritoneal cavity and even the bloodstream, plays an important role in perpetuating the inflammatory cascade that underlies multiple organ dysfunction. This is observed when the protective barrier normally provided by the wall of the gut is breached. The problem is markedly worsened in the presence of associated liver cell dysfunction. In fact when ARDS occurs against the background of liver cell failure, death invariably results.

INVESTIGATIONS (BOX 1)

Chest X-Ray

The chest radiograph shows interstitial edema in the early stages and full-blown pulmonary edema in established cases. The pulmonary edema causes bilaterally symmetrical shadowing, but the shadowing may initially be predominantly unilateral, depending on the position of the patient. The absence of cardiomegaly, of Kerley's lines and of vascular redistribution towards the upper lobes, help distinguish the pattern from cardiogenic pulmonary edema. The absence of lobar consolidation helps differentiate it from infection. Having said this, cardiac failure, pneumonia and pulmonary emboli may all cause diagnostic confusion. ARDS does not necessarily involve both lungs symmetrically; one lung may be considerably more involved than the other. This adds to the problem of effective ventilation.

Arterial Blood Gases

Blood gas estimation is essential in the initial diagnosis and subsequent monitoring of ALI. In the initial stages, varying degrees of hypoxia are seen with hypocapnia. In late stages, hypercapnia may be seen. The pH disturbances range from respiratory alkalosis in the initial stages, to respiratory acidosis and metabolic acidosis in the later stages. The hypoxia is refractory to supplemental oxygen, indicating that in addition to ventilation-perfusion mismatch, increased right to left shunt and dead space ventilation also play major roles.

Box 1: Investigations in acute lung injury/acute respiratory distress syndrome (ALI/ARDS)

- Chest X-ray
- Arterial pH and blood gases
- Hemodynamic measurements using a Swan-Ganz catheter in selected cases
- Pulmonary compliance
- Routine biochemistry to evaluate other organ dysfunction
- Full bacteriological screen—
  - Blood culture
  - Urine culture
  - Culture of tracheal aspirates
  - Culture of bronchoalveolar lavage (BAL)
  - Culture of any other secretions/discharges

Hemodynamic Measurements

The insertion of a Swan-Ganz catheter is not essential for the diagnosis of ALI; however, it may on occasion be the only way to conclusively distinguish ALI from cardiogenic pulmonary edema. Insertion of a Swan-Ganz catheter may also prove invaluable in the management of an individual patient. Much has been written concerning the wisdom of invasive monitoring in such patients, and there are some who feel that this technology may itself contribute to poor patient outcome. We now use the Swan-Ganz catheter infrequently. A Swan-Ganz catheter should only be inserted by doctors familiar with its use to obtain specific answers to specific diagnostic or therapeutic dilemmas—for example, assessing the adequacy of volume resuscitation, for titrating inotropic support, for assessing left ventricular dysfunction, degree of intrapulmonary shunting or assessing adequacy of DO_2 in problem patients.

Pulmonary edema with pulmonary wedge pressure less than 18 mm Hg in the presence of a normal colloid oncotic pressure is diagnostic of ALI (ARDS).[18] It should be noted that estimations of wedge pressure may be affected by the position of the catheter tip (which should be below the left atrium in zone 3 lung), and the presence or absence of PEEP. All patients, ill enough to require a Swan-Ganz catheter, are ill enough to require at least 10 cm H_2O of PEEP. In critically ill hypoxemic patients, it may not be wise to switch off PEEP even while the necessary hemodynamic measurements are being made. Some authors have advocated subtracting 50% of the PEEP value from the measured wedge pressure, but a study by Teboul and associates[19] suggested that PEEP did not affect the correlation between wedge pressure and left ventricular end-diastolic measurements, even in patients with severe ALI. To avoid iatrogenic complications, we prefer to remove a Swan-Ganz catheter within 3 days.

Pulmonary Compliance

Lung compliance is usually decreased to less than 30 mL/cm H_2O. Compliance can easily be measured in patients on mechanical ventilator support.

Routine Tests

Tests for evidence of other organ dysfunction, e.g. renal, hepatic, hematological parameters, should be done.

Full Bacteriological Screen

This should include blood culture, cultures of tracheal aspirates and in some patients with nosocomial pneumonia, culture of bronchoalveolar lavage fluid or culture of protected brush samples obtained bronchoscopically to determine the nature of the infecting organism. Cultures of urine and other body secretions and discharges are also necessary.

MORTALITY AND PROGNOSIS

Some studies suggest a fall in mortality figures in ARDS compared to earlier years. But mortality depends on the population under study. Even in the ARDS network study[20] of 861 patients, the mortality of 31% in the group using lung protection measures (6 mL/kg V_T) is significantly underestimated because many severely ill patients were excluded—those with advanced liver disease, bone marrow transplant, severe chronic respiratory disease, burns greater than 30% body surface area (BSA) and those not expected to live more than 6 months.

Mortality remains quite high on population based studies. Several multicenter studies in France,[21] Sweden,[22] Australia,[23] and Argentina[24] defined mortality and prognostic variables in observational population based studies rather than clinical trial participants. Mortality varied—32% in ALI to 58–60% in ARDS. The highest mortality, close to 60%, was from the French study.

In other studies, mortality was highest in sepsis (43%), intermediate in pneumonia (36%) or aspiration (37%), lowest in multiple trauma (11%). Low tidal volumes were effective in reducing mortality across all cases of ALI/ARDS.[25]

Four factors determine prognosis in ALI/ARDS—

1. Severity of the lung injury (judged by PaO_2/FiO_2 ratio).
2. Nature and severity of the precipitating factor.
3. Presence and degree of dysfunction of other organ systems.
4. Background or associated disease.

In our experience, prognosis depends less on the severity of ALI and more on the other three factors listed above. Uncontrollable sepsis, particularly uncontrollable intra-abdominal sepsis, has a hopeless prognosis with a 100% mortality. Severe sepsis even when controlled can set into motion a chain of events that may carry a mortality of greater than 60%. Prognosis is worse in the presence of septic shock. On the other hand, direct injury to the lungs as in drowning, inhalation of noxious fumes, mild to moderate aspiration of gastric contents, in our experience, has a mortality of less than 20%, provided there is no nosocomial infection and no other major complication. Severe nosocomial pneumonia occurring in ARDS has a mortality of about 30%.

In the West,[26] the reported mortality for single organ failure is 15–30%, for two organ failure it is 45–55%, and for three or more organ failures lasting for more than 4 days, greater than 85%. In our experience, we have found this true only for Gram-negative sepsis. These figures are unnecessarily pessimistic and are not true when multiple organ failure complicates fulminant *P. falciparum* infection, fulminant tetanus and other severe tropical infections. Fulminant tetanus with excellent intensive care has a mortality of less than 10%, and in fulminant *P. falciparum* infection the mortality even with severe prolonged multiple organ dysfunction is below 30%.

MANAGEMENT

Despite the many recent advances in intensive care, severe ARDS continues to carry an overall mortality of 30–60%. As mentioned earlier, patients with ALI and ARDS do not usually die of respiratory failure (only 16% of all deaths in one large series were due to refractory hypoxemia and hypercapnia).[27] The majority of patients die of sepsis and multiple organ failure. Intensive care is mandatory for efficient management. The following management principles apply—

Treatment of the Underlying Condition

This should be identified promptly and treated aggressively. Unfortunately the treatment of many diseases causing ARDS is largely supportive. Sepsis is an important exception and should be promptly recognized and treated. Studies have shown that the prompt use of an appropriate antibiotic or antibiotics significantly improves morbidity and mortality. Surgical drainage of an abscess and prompt surgery for abdominal sepsis are mandatory. Specific therapy for fulminant tropical problems causing ARDS should be immediate—in particular the use of artemisinin and/or quinine for severe *P. falciparum* infections.

Respiratory Support

This forms the cornerstone in the management of ALI and ARDS. Yet it needs to be stressed that mechanical ventilation is purely supportive, allowing the lungs time to recover from the acute insult. Mechanical ventilation in patients with severe ALI (ARDS) presents complex problems and difficulties. To be effective, the intensivist must be aware of the changes in cardiorespiratory physiopathology, the interaction between the heart and the lungs, the importance not only of effective gas exchange but also of efficient DO_2 and the dangers and complications of ventilator support.

Initiating Ventilator Support

There are two important indications for initiating ventilator support in an evolving ARDS. The first is progressive hypoxemia not responding to oxygen inhalation; the second is a marked, unsustainable increase in the work of breathing, as when the respiratory rate is greater than 35–40/minute and

the minute-volume exceeds 12 L/minute. A lowered lung compliance adds even more to the work of breathing. Under the above circumstances, it is best to electively intubate and initiate ventilatory support even if the PaO_2 is greater than 60 mm Hg on supplemental oxygen. Elective intubation and ventilatory support are also preferred in the presence of hemodynamic instability, and if for any reason the patient is unable to maintain and protect the airway.

Noninvasive Ventilator Support

Severe ALI (ARDS) always needs intubation and mechanical ventilation. A very small subset of patients with mild ALI may however be adequately oxygenated with the help of continuous positive airway pressure (CPAP) or by the use of a bilevel positive airway pressure (BiPAP) ventilator, using a tight fitting face mask. A recent multicenter observational study[28] has reported the merits of noninvasive ventilation (NIV) in early ARDS from three ICUs in Italy and Spain. One-third of the patients were given NIV (the remaining two-thirds were already intubated and ventilated). The NIV patients had less ventilator-associated pneumonias and a lower mortality. This was not a randomized controlled trial, and though the study showed that NIV was effective in early cases, no definite conclusions are possible.

If NIV is decided upon, CPAP levels are kept between 10 cm and 12 cm of H_2O. In order to maintain intrathoracic pressure at the required level of CPAP throughout the respiratory cycle, high gas flows in excess of 70 L/minute are required. With a BiPAP machine, reasonable initial ventilator settings are expiratory positive airway pressure (EPAP) of 7–10 cm H_2O and inspiratory positive airway pressure (IPAP) of around 15–18 cm, the settings being adjusted both for patient comfort and for providing and maintaining an arterial oxygen saturation of greater than 90%. Noninvasive mechanical ventilation in patients with mild ALI recruits collapsed alveoli, increases the FRC and lung compliance, thereby unloading the respiratory muscles and reducing the work of breathing. A good response to noninvasive positive pressure ventilation is generally observed within 30 minutes of its initiation and is characterized by improved oxygen saturation, a fall in respiratory rate and less patient distress. An inability to maintain SaO_2 to greater than or equal to 90% or the presence of hemodynamic instability or a worsening clinical state are indications for intubation and mechanical ventilation.

Dangers of Endotracheal Intubation in ALI and ARDS

The major danger during intubation is a severe increase in hypoxia, in an individual who is already hypoxic to start with. Hemodynamic instability and the danger of gastric aspiration form additional risks during intubation.

Endotracheal intubation should therefore be performed by an expert, preferably with the patient awake, using mild sedation with a benzodiazepine or a narcotic. In an acute crisis, succinylcholine along with intravenous propofol may be used.

Changing of the endotracheal tube in a patient with ARDS following rupture of the cuff or due to obstruction of the tube is also risky. A sudden loss of PEEP during this procedure may cause rapid desaturation with dangerous sequelae.

Principles of Mechanical Ventilation[29]

The last several years have seen the evolution of two fundamental concepts in the ventilatory support of patients with ARDS. First is the prevention of overdistension of the alveoli by limiting V_T and the pause pressure. Second is to choose a level of PEEP which is sufficiently high to prevent derecruitment of the alveoli at end expiration. *The fundamental concepts that guide ventilator support in ARDS are these two lung protection goals.* Avoidance of oxygen toxicity to the lungs and prevention of hemodynamic instability of the cardiovascular system are two other important conditions guiding ventilator support in these patients.

Limiting tidal volume The lung protection strategies have been firmly established following the result of the landmark ARDS Clinical Trials Network.[20] In this large prospective RCT, patients were randomly assigned to receive a V_T of 6 mL/kg of predicted body weight or 12 mL/kg of predicted body weight. The plateau pressure (the airway pressure under no flow conditions maintaining the V_T) in those receiving V_T of 6 mL/kg was not to exceed 30 cm H_2O. If it did so, the V_T was further reduced to 5 mL/kg of predicted body weight or even to a minimum of 4 mL/kg of predicted body weight. Patients receiving the lower V_T had a lower mortality (31%) compared to those receiving higher V_T (mortality 40%). There was relative reduction in mortality of 22%.

The established principle is therefore to use low tidal volumes (6 mL/kg) and ensure that the pause pressure does not exceed 30 cm of H_2O when using a volume regulated mode of ventilatory support. This strategy prevents overdistension of alveoli and undue increase in intra-alveolar pressure. In fact, large tidal volumes (10–15 mL/kg) in patients with ARDS are dangerous. It is accepted that overdistension of alveoli in these patients can cause an amplification of the already existing lung injury (volutrauma), presumably by increasing edema and pulmonary cytokine production. In addition to volutrauma, high intra-alveolar end-inspiratory pressures can lead to an increased incidence of barotraumas. The concept of barotrauma is not new, but its spectrum includes not just pneumothorax, but also pneumomediastinum, interstitial emphysema, subcutaneous emphysema and pulmonary hemorrhage. A frequent consequence of a limitation of the V_T in the above manner is a rise in the $PaCO_2$ to above 40 mm Hg. The $PaCO_2$ is allowed to rise—a condition called permissive hypercapnia.

The difference in mortality between the low V_T group and the high V_T group in the ARDS network trial was related to a greater reduction in IL-6 levels in patients with low V_T. Ranieri and coworkers[30] have also shown lower levels of TNF, IL-1, IL-6 and IL-8 in the bronchoalveolar lavage fluid of patients treated with the lung-protective ventilatory strategies, when

compared to patients treated with the more conventional ventilatory techniques. These cytokines can produce further lung injury; they also gain entry into the bloodstream and produce injury at distant sites, perhaps contributing to multiple organ dysfunction and multiple organ failure.

Use of PEEP

Positive end-expiratory pressure is not a new ventilatory strategy but a mainstay of oxygenation in ALI and ARDS ever since the original description of the syndrome. It acts by recruiting collapsed alveoli, restoring FRC to normal and thus increasing compliance. It also causes redistribution of lung water within the alveolar space, improving ventilation/perfusion (V/Q) mismatch and decreasing the shunt and venous admixture. By improving oxygenation, PEEP allows the oxygen concentration delivered to the patient to be reduced, thus decreasing the chances of oxygen toxicity, which in itself can worsen lung injury.

Of recent interest, is the likelihood that PEEP, if properly adjusted, also prevents further lung injury during mechanical ventilation of patients with ARDS. How does it do so? The concertina effect of opening of the alveoli during the inspiratory phase of mechanical ventilation, followed by well-nigh total closure of alveoli during the expiratory derecruitment, generates strong shear forces that worsen and perpetuate lung injury. Choosing the exact level of PEEP that can prevent the derecruitment of alveoli during mechanical ventilation is a difficult but an important lung protection goal in patients with ALI and ARDS. In the ARDS network trial, the level of PEEP and FiO_2 was adjusted with a predetermined PaO_2/FiO_2 ratio in a stepwise fashion, so as to keep the PaO_2 and SaO_2 at a satisfactory desired range. Ideally PEEP should be individualized for each patient. One can attempt to do so by plotting the pressure volume curve in a given patient, noting the upper and lower inflection points and adjusting the PEEP level at 1–2 cm above the lower inflection point. There is however often an observer difference in determining the exact lower inflection point (which is a slope rather than a point). Again the pressure-volume curve relates to the whole of the lung but does not reflect regional differences (some alveoli are overdistend, others collapsed or consolidated). It is obvious that PEEP is more likely to be useful in patients with ARDS where a good proportion of the affected lungs are recruitable. On the other hand, if in a patient the recruitable lung is very small, PEEP will be of little use. In fact, it may be harmful as it may only serve to overdistend alveoli and thus contribute to lung injury. Gattinoni determined the degree of recruitability of lungs through CT studies, a luxury denied to most ICUs in the developing world. Perhaps the simplest approach is to use the least PEEP that provides adequate oxygenation at an FiO_2 of less than 0.6, starting with a PEEP of 10 cm and as far as possible not exceeding 15 cm, as the risk of barotrauma particularly in Indian patients is then significant. If oxygenation does not improve as judged by the PaO_2/FiO_2 ratio, and if there is no increase in compliance, PEEP should be reduced and not allowed to exceed 5 cm H_2O.[31]

Three large randomized control trials (ARDS network trial, LOV study, ExPress study)[32,33] have compared the effects of higher PEEP to lower PEEP levels. All demonstrated increased oxygenation in the higher PEEP group, but there was neither a decrease in mortality nor in ventilator free days. This suggests that the use of modest PEEP levels is to be generally preferred and is adequate to prevent ventilator-induced lung injury. High PEEP may perhaps open more atelectatic alveoli but overdistended normal alveoli, contributing further to lung injury.

Ventilator Modes

There are a large number of modes offered by currently available ventilators. These include volume control ventilation, pressure control ventilation, airway pressure release ventilation, high-frequency oscillatory ventilation (HFOV) and open lung ventilation. Whichever mode one uses, the focus should be on preventing alveolar overdistension, countering alveolar derecruitment, minimizing cardiovascular instability and avoiding oxygen toxicity. The volume controlled mode (with lung protection strategies) was used in the ARDS network trial and remains the one most commonly adopted. There is no evidence to suggest that any of the other ventilatory modes are superior to the volume controlled mode in the management of ARDS. Many units use the pressure controlled mode; it is important when using this mode to ensure low V_T (6 mL/kg body weight) and not to exceed a peak pressures of 30 cm H_2O. Inverse ratio respiration has been used generally with pressure controlled ventilatory support. The inspiration expiration ratio should be preferably 1:2 or 1:1 and not lower. The increased inspiratory time may allow better oxygenation in these patients.

High-frequency oscillatory ventilation theoretically should offer lung protection as the tidal volumes delivered are very small (less than the dead space) and at a high frequency, gas exchange being promoted by diffusion. Its efficacy as a ventilatory mode in children is generally accepted. It remains to be established whether it reduces morbidity and mortality in ARDS when compared to the lung protection strategies adopted with the volume controlled mode. A multicenter RCT studying HFOV called the Oscillation for ARDS Treated Early (OSCILLATE) Trial Pilot Study organized by Canadian Critical Care Trials Group (CCCTG) has been completed.[34] It concludes that in adults with moderate to severe ARDS, early application of HFOV, as compared to low tidal volume ventilation with a high PEEP, does not reduce, and may increase the in-hospital mortality.

Use of Prone Position

The prone position was used to improve oxygenation in ARDS within a decade of the first clinical description of this syndrome. When patients are in the prone position as compared to the supine position, oxygenation improves in over 60% of patients with oxygen ratios (PaO_2/FiO_2) being significantly higher. This improvement in oxygenation is due

to an increase in the functional residual capacity, decreased atelectasis and improved ventilation perfusion ratios. Briefly, the prone position results in improved oxygenation by increasing functional lung. However, despite improved oxygenation, several randomized trials in the past have shown that the prone positioning did not reduce overall mortality.

In contrast to the previous studies, Guerin and colleagues[35] have recently reported excellent results in the Proning Severe ARDS Patients (PROSEVA) randomized trial. This was a multicenter trial of prone ventilation in patients with severe ARDS. The 28-day mortality with prone positioning had halved (16% vs 32.8% with supine ventilation), an excellent treatment effect. Prone position was applied for 73% of the available time, patients being returned to the supine position once a day, whereas in the previous trials prone position was applied merely 30% of the day. In the PROSEVA trial prone position resulted in better oxygenation, lower oxygen requirements and more ventilation-free days. The mortality among controls (32.8%) was similar to the mortality of 25–40% observed in various previous trials.[36]

These results cannot be ignored. There are however two caveats: (1) the study group in the PROSEVA trial was a highly selective group of severe ARDS patients and (2) the prone position, though conceptually simple, poses many challenges in nursing and patient management. It can lead to various problems—kinking, dislodgement of the airway, intravascular lines, drainage tubes, as also serious pressure sores on the face. It should therefore be attempted only in units trained to manage prone-positioned patients.

It appears from the work of Guerin and colleagues[35] that the prone position used early in the natural history of severe ARDS, for the greater part of the day, significantly reduces mortality. These results however need to be confirmed by other centers.

Permissive Hypercapnia

When patients with ARDS are ventilated with the lung protection goal of low V_T and pressure limited ventilation, alveolar hypoventilation frequently occurs, causing a rise in $PaCO_2$ to 60–70 mm Hg or even more. Increasing $PaCO_2$ with respiratory acidosis can have potential adverse physiological effects such as arrhythmias, cardiovascular and central nervous system depression. However, these effects are not generally encountered in clinical practice. In fact, high $PaCO_2$ levels seem to be very well-tolerated in adequately sedated patients. Most clinicians and intensivists favor permissive hypercapnia to the injurious effects of overdistended alveoli and high inspiratory inflation pressures. The $PaCO_2$ in permissive hypercapnia should preferably be allowed to rise slowly at the rate of 10 mm Hg/hour. Hypercapnia needs correction only if there is a significant fall in the pH. In the ARDS network trial, if the pH fell to less than 7.30, the respiratory was rate was increased till the pH was greater than 7.30 or the respiratory rate equaled 35/minute. If the pH was less than 7.3 in spite of the respiratory rate being increased to 35/minute, an IV bicarbonate infusion was administered. IV bicarbonate may temporarily correct the pH but could add substantially to the CO_2 that needs to be excreted by the patient via the lungs. IV sodium bicarbonate could also lead to volume overload and potassium depletion in critically ill patients who already have an increase in intrapulmonary extravascular water content.

Open Lung Concept

The open lung concept though described first by Lachmann in 1977 has been adopted as a ventilatory strategy for ARDS over a little more than two decades. Gattinoni and coworkers[37] showed that patients with ARDS had multiple areas of atelectasis chiefly in the dependent lung regions, due to reduced volume of the aerated lung. The ventilatory strategy of an open lung opens up the atelectatic areas and keeps them open. Thereby the cyclic shear forces of alveolar opening and closing are minimized and optimal gas exchange is achieved (PaO_2 >450 mm Hg on an FiO_2 of 1). The open lung procedure is always attempted using pressure controlled ventilation with an inspiratory to expiratory (I:E) ratio of 1:1 and with an FiO_2 of 1. To start with PEEP is applied at 15–20 cm H_2O in patients with ARDS, and the lung is opened with slow progressive increase (by 2 cm at a time) in the peak inspiratory pressure up to 40–60 cm H_2O. The opening pressure is the peak inspiratory pressure at which the lung is "opened". The success of recruitment of closed alveoli is gauged either by noting the sudden sharp increase in PaO_2 greater than 450 mm Hg when the lung fully opens up or by the proportional increase in V_T following increase in the peak inspiratory pressure. The peak inspiratory pressure and PEEP are now adjusted to the lowest pressure which keeps the lung open. This lowest pressure is realized when the V_T is stable and the arterial blood gases continue to show a high constant PaO_2. The ideal pressure is generally 15–30 cm H_2O less than the required recruitment opening peak pressure. After opening the lung and finding the lowest pressure to keep it open, the resultant pressure amplitude is minimized and gas exchange maximized. The ventilatory strategy described above enables a reduction in FiO_2 and protects the lung from further injury. It is possible that an open lung is less likely to produce cytokines injurious to itself as also to other organ systems. Transient hypotension and transient desaturation are the most commonly observed side effects during recruitment maneuvers. Serious adverse effects which include barotraumas (1%) and arrhythmias are infrequent.

The open lung strategy, if adopted, should preferably be put to use in the first 24–48 hours of mechanical ventilation in ARDS. Amato and coworkers[38] showed a reduced mortality in ARDS patients using the open lung ventilatory strategy as compared to ARDS patients on conventional modes. The Lung Open Ventilation Study (LOVS)[32] compared the ARDS network protocol to a regimen using pressure controlled ventilation, recruitment maneuvers combined with levels of PEEP of 5–7 cm higher for a given PaO_2 than that used in the ARDS network trial. There was no statistically significant increase in survival in the interventional arm, though no adverse effects were observed.

On current evidence,[39] the routine use of recruitment maneuvers cannot be either recommended or discouraged. Recruitment maneuvers should be considered on an individualized basis in patients with ARDS who have severe life-threatening hypoxia. It is possible that the chief benefit of open lung ventilation may be related more to the low V_T and low peak pressure during ventilation rather than in opening the lung.

Use of Extracorporeal Membrane Oxygenation for ARDS in Adults

Recent advances with extracorporeal membrane oxygenation (ECMO) in the successful management of severe ARDS during the 2009 H1N1 influenza A epidemic has resulted in a renewed interest in this technique.

The only controlled clinical trial comparing ECMO technology versus conventional mechanical ventilation in the management of ARDS is the CESAR trial[40] to which the reader is referred for further details. In this trial, death or severe disability at 6 months occurred in 37% of patients referred for consideration for ECMO, versus 53% for the assigned to management by conventional ventilation. This study was however not a randomized study and the results must be interpreted with caution.

The indications and contraindications for ECMO in severe ARDS are tabulated in Box 2.

It is important that ECMO is undertaken in specialized centers that have experience with this technique. Details of this technique are outside the scope of this book. The reader is referred to the CESAR trial.

Box 2: Indications and contraindications for ECMO in severe ARDS

Indications—
- Severe hypoxemia (PaO_2/FiO_2 <80 despite 15–20 cm PEEP for at least 6 hours in potentially reversible respiratory failure)
- Uncompensated hypercapnia (pH <7.1) in spite of optimal management
- Very high end-inspiratory plateau pressure (>35–45 cm H_2O) despite optimal ventilator management

Contraindications—
- A very high end-inspiratory plateau pressure (>35–40 cm H_2O) or an FiO_2 (>80%) for >7 days
- Unavailable or limited access
- Irreversible organ dysfunction (e.g. brain injury)
- Any condition that contraindicates use of anticoagulant therapy

Other Measures

Fluid balance It is important not to overhydrate the patient as this worsens pulmonary edema. In established ALI/ARDS, we have always preferred to keep filling pressures of the left ventricle on the lesser side of normal (PAOP <12 mm Hg), central venous pressure (CVP) not more than 6 mm Hg provided perfusion of vital organs is satisfactory. The ARDS Network Fluid and Catheter Treatment trial[41] has recently shown that a conservative fluid management strategy increased the mean number of ventilator free days (14.8 vs 12.1). There was a 2.9% reduction in mortality rate in the conservative arm but this was not statistically significant. This study showed that the conservative fluid strategy did not increase the incidence of renal failure or shock. Also, the use of a pulmonary artery catheter or a central venous catheter in monitoring management was associated with the same mortality.

The above strategy applies to patients who are not in shock or whose shock has been effectively countered with appropriate fluid management. Unquestionably a patient in shock will require the initial fluid resuscitation emergency measures outlined in the Chapter Sepsis and Septic Shock.

Other fluid management strategies In the particular setting of hypoproteinemia and ALI/ARDS, the combination therapy of albumin and furosemide may be useful in improving pulmonary physiology.[42] There is however no evidence that outcome is favorably influenced. Hypoproteinemia is a documented risk factor in the development of ALI/ARDS as also for poor outcome in critical illness in general. This in our opinion is reason enough to counter hypoalbuminemia with infusions of albumin in patients with ARDS.

Circulatory support It is important to ensure adequate DO_2 or delivery to the tissues. DO_2 is not only dependent on an adequate PaO_2, but is also dependent on cardiac output and the hemoglobin (Hb) concentration. The Hb concentration should be kept around 10 g/dL with a hematocrit of 35%. Inotropic support should be given even in patients with moderate lung injury. Dobutamine is preferred if the cardiac output is low as it generally does not induce tachycardia. If the systolic blood pressure is less than 90 mm Hg, or if the systemic vascular resistance is low, dopamine is to be preferred. Norepinephrine is often necessary in hypotensive patients.

Supramaximal DO_2 (cardiac index >4.5 L/min/m^2 and DO_2 above 600 mL/min/m^2) was earlier thought to reduce oxygen debt in the tissues, prevent hypoxic injury and organ system failure. This is however by no means certain. It is possible that increasing DO_2 to supramaximal levels reduces mortality in just a subgroup of patients, such as high-risk surgical patients. In our experience and in the experience of most critical care units, supramaximal DO_2 does not reduce mortality in ALI. Volume loading patients with ARDS to maintain PAOP at upper normal limits (15–18 mm Hg) in an attempt to raise the cardiac output, invariably does harm by potentiating the lung injury.

Support to Other Organ Systems

All organ systems often need support, in particular the kidney. Ultrafiltration or dialysis may be necessary to treat volume overload or renal failure.

Nutritional Support

Good nutrition is vital, particularly when ARDS is due to excessively catabolic states as in fulminant tetanus, burns or severe sepsis. Severely catabolic states require a caloric intake of 2,500 or more calories/day, and this could lead to excessive fluid intake in a clinical situation which often necessitates fluid restriction. Under these circumstances, nutritional requirements are sacrificed on a short-term basis to allow fluid restriction. The alternative is to remove additional water by the use of loop diuretics if renal function is good, or by the use of ultrafiltration if renal function is impaired. Enteral feeding is always to be preferred. In the presence of ileus, abdominal sepsis, parenteral feeding becomes necessary.

Prophylaxis for stress ulcers and for venous thromboembolism is important.

Treatment of Complications

These can involve any organ system; they should be promptly diagnosed and treated. Iatrogenic sepsis and nosocomial pneumonias are of ominous significance.

Role of Corticosteroids in ARDS

There continues to be a raging controversy whether low-dose corticosteroids can reduce morbidity and mortality of ALI and ARDS, without increasing the risk of adverse reactions. A number of trials have evaluated the role of corticosteroids in the treatment of ARDS at various stages. It appears that in the late stage of ARDS corticosteroids have no benefit and are associated with adverse outcomes. Use of corticosteroids in early ARDS showed a reduction in organ dysfunction score, lung injury score, ventilator requirement and intensive care stay. There was however no definite evidence of significant reduction in mortality. Most of these trials have been small and have marked heterogeneity. We feel that the role of corticosteroids in ARDS is not convincingly proven to be beneficial. If used it should be restricted to the early stage of ARDS and given in a dose of not more than 50–100 mg 8 hourly of hydrocortisone intravenously. The debate on whether to use or not use corticosteroids in ARDS is likely to continue.[43]

New Potential Therapies for ARDS

Granulocyte-macrophage colony-stimulating factor (GM-CSF) This is another therapy being evaluated as possible treatment for ARDS. GM-CSF is believed to encourage homeostasis of alveolar macrophages and to prevent apoptosis of alveolar epithelium. Further studies will decide the value of this therapy.[44]

Use of beta-2 agonists Beta-2 agonists have been reported to accelerate resolution of pulmonary edema in clinical and experimental studies and hence it was hypothetical that aerosolized beta-2 agonists would improve clinical outcomes in acute lung injuries. However, a multicenter randomized placebo-controlled clinical trial in 282 ALI patients receiving mechanical ventilation showed that aerosolized albuterol did not improve clinical outcome. Their use therefore is not recommended.[45]

Other pharmaceutics measures A great deal of research continues on pharmaceutical measures that could reduce or counter the inflammatory cascade that initiates and perpetuates injury to the lung and other organ systems. The use of anticytokines, anti-TNF antibodies, soluble TNF receptors and cyclooxygenase inhibitors is of unproven benefit. Surfactant replacement, nitric oxide inhalation, platelet-activating factor antagonist, pentoxifylline and anti-proteases have all proved of no avail. None of these drugs can be recommended at this stage.

Immunonutrition Immunonutrition has attracted attention in recent years. Addition of linoleic acid to the diet, as also arginine, glutamine, nucleotides and omega fatty acids, is reported to reduce infection rates in critically ill patients treated with enteral immune-enhanced diets. There is no evidence that these diets influence ultimate outcome.

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CHAPTER 33

Acute Severe Asthma

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INTRODUCTION

Acute severe asthma is characterized by a severe asthmatic attack unrelieved by the repeated use of aerosolized bronchodilators. It is a medical emergency that spells danger and should never be underestimated.[1] Considering that asthma is a widely prevalent disease with incidence rates in the West of around 10% in school children, and around 4–5% in adults, deaths from asthma are relatively rare. What is of more significance is that despite asthma being by definition a reversible disease, deaths still occur with predictable frequency. Data from this country is not available, but in the UK, 2,000–4,000 people die of asthma every year. There is no evidence that the death rate is declining, in fact, most recent studies show that it is on the increase. This increase in death rate applies to every age group and is rising by approximately 4.5% per annum in the 5–34 year age group. An asthma death is always a cause for introspection, because it generally affects previously healthy young adults with no background of other illness. It becomes even more poignant when one reviews the asthma death-audits available. Most of these studies clearly show that up to 80% of all asthma deaths are related to lapses on the part of the patient and the doctor, and are thus potentially preventable. Education of the public and the medical profession is essential in preventing many of these deaths. Some of the patient and doctor related factors that may contribute to asthma deaths are tabulated in Box 1.[2]

Box 1: Points emerging from asthma death studies 1968–1987[3]

I. Patient-Related Factors—
- Most patients dying from asthma have a long history of asthma
- Most have had multiple admissions to hospitals
- Patient compliance is poor
- Patients accustomed to a degree of disability
- Patients unable to gauge severity of an attack
- Underuse of peak flow meters
- Poor control for days/weeks prior to fatal attack

II. Doctor-Related Factors—
- Doctors underestimate severity of the attack
- Objective measurements (PEF, ABG) not made
- Underuse of steroids
- Underuse of beta-agonists
- Overuse of beta-agonists
- Injudicious use of sedatives
- Beta-blockers always contraindicated
- Theophylline levels not monitored

Abbreviations: PEF, peak expiratory flow; ABG, arterial blood gas.

PATHOPHYSIOLOGY OF AN ACUTE SEVERE ASTHMA ATTACK[1]

The airway obstruction in asthma is widespread but uneven in its distribution. It is caused by a combination of thick tenacious mucus-plugging of the smaller airways, bronchial mucosal inflammation and edema, and smooth muscle spasm. The more severe the asthma attack, the greater the tendency to closure of the airways at higher than normal lung volumes. The increase in lung volumes raises the static transpulmonary pressure and results in an increased outward radial traction on the airways that attempts to keep them open. The airway obstruction is reflected in falling peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1), whilst the increasing lung volume is recognized clinically

and radiologically by a hyperinflated chest, and physiologically by a markedly increased residual volume (RV), functional residual capacity (FRC), total lung capacity (TLC) and RV/TLC. During recovery, hyperinflation may resolve with a fall in TLC occurring before there is much increase in FEV_1 or PEF.

The combination of advanced airway obstruction and hyperinflation results in markedly increased work of breathing. The extreme dyspnea experienced by an asthmatic is a reflection of the difficulty experienced in breathing at high lung volumes for prolonged periods of time. The work of breathing during a severe attack of asthma is estimated at 5–25 times than that performed by normal adults at rest.

The gas exchange abnormalities and the hypoxemia in asthma are a consequence of ventilation-perfusion imbalance. The degree of hypoxemia correlates with the severity of airways obstruction and hence the number of low ventilation/perfusion (V/Q) units. Flenley observed that a partial pressure of oxygen in arterial blood (PaO_2) below 60 mm Hg was usually associated with an FEV_1 of less than 0.5 L.[4] In some lung units the airway obstruction may be complete (e.g. airways in that area completely blocked off by mucus plugs) and then a right to left shunt (Q_S/Q_T) may contribute to the hypoxemia.

In a mild attack or the initial phase of a severe attack, the primary gas exchange problem is hypoxemia accompanied by hypocapnia. The latter reflects the increased alveolar ventilation induced by hypoxia and anxiety. As the attack evolves and airway obstruction worsens, the partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) starts to rise. Whilst the incidence of hypercapnia is low, prompt identification is critical because of the frequent need for mechanical ventilation at this stage. Respiratory acidosis and lactic acidosis are also grave prognostic signs.[3]

CLINICAL FEATURES

The *onset* of an acute severe asthma attack can be dramatic, for example, in the atopic patient suddenly exposed to high concentrations of a provocating allergen, or in a patient markedly sensitive to aspirin. Such a patient may have a catastrophically sudden attack with extreme chest tightness and inability to breathe. More often the acute attack may have been building up over several hours, days or even weeks before the patient is hospitalized. A study by Bellany and Collins revealed that 50% of patients dying of asthma in hospital had been waking up for 5 nights a week, in the week prior to death and as many as 35% had been waking up that often in the previous month.[5] Clearly an intensification of their treatment at this stage (for example, with a short oral course of steroids) might have prevented the fatal attack.

A *history* of wheeze at night, bad enough to wake the patient up, must always be elicited. Worsening of exertional dyspnea and increasing requirement of inhaled beta-agonists with less relief after each puff, are also pointers to a severe attack. The longer the delay in initiating effective therapy and the more protracted the attack, the worse the prognosis in acute severe asthma.

Box 2: Features of a severe attack of asthma

- Inability to complete sentence in one breath
- Disturbance in level of consciousness
- Respiratory rate ≥30/min
- Silent chest
- Cyanosis
- Respiratory muscle fatigue
- Tachycardia ≥110/min
- Systolic paradox ≥15 mm Hg
- PEF ≤30% of predicted or known best
- PaO_2 <60 mm Hg despite supplemental oxygen at 60% FiO_2
- $PaCO_2$ which is normal or high, and rising

Note: Not all these features are necessarily present in a patient.

Abbreviations: PEF, peak expiratory flow; PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood.

On examination, the patient is distressed and able to speak in short sentences only. He gasps for breath, each breath being accompanied by loud wheezing and sometimes uncontrollable coughing. He is unable to lie flat and usually sits upright or leans forward struggling to breathe. A respiratory rate of 30 breaths per minute or more is a bad prognostic sign. On auscultation of the chest, most patients have loud, widespread inspiratory and expiratory rhonchi, but the occasional patient with severe asthma has a silent chest with hardly any audible breath sounds or rhonchi.[1] A silent chest is another grave prognostic sign and denotes obstruction so severe that there is hardly any airflow. Accessory muscles of respiration are in active use as the patient struggles to overcome the airway obstruction by sternocleidomastoid contraction and intercostal retraction. Cyanosis may be difficult to detect but when present denotes a severe and dangerous attack. Tachycardia is always present and may be worsened by the medication the patient has already taken or received to ward off the attack. A pulse rate over 110 beats per minute denotes a severe attack. The presence of a significant pulsus paradoxus has been shown to reflect lung hyperinflation combined with wide fluctuations in intrathoracic pressure, and when more than 15 mm Hg, reflects a severe attack (Box 2).[1]

DIFFERENTIAL DIAGNOSIS[6]

The axiom "all that wheezes is not asthma" must never be forgotten. Some of the asthma masqueraders are cases of acute left ventricular failure (cardiac asthma), tracheal or large airway obstruction, bronchiolitis, pulmonary eosinophilia, pulmonary embolism, sarcoidosis, carcinoid syndrome, angioneurotic edema, laryngeal spasm (vocal cord spasm) and factitious asthma. In a child admitted to the intensive care unit (ICU) for a first episode of asthma, the possibility of a foreign body obstructing the airway should always be entertained.

MONITORING

Peak Flow Rate

Peak flow rate (PFR) is the most essential, but least frequently performed monitoring test. Peak flow meters are cheap, easily available and portable, and should be present in every doctor's office, casualty department, hospital ward and ICU. Even in a very tachypneic patient a peak flow maneuver can be performed at the bedside (unlike an FEV_1 maneuver), and gives objective evidence of the severity of an asthmatic attack. The peak flow must be measured on admission to the ICU; a PFR less than 30% of the predicted normal or known best, signifies a severe attack. Thereafter, peak flow is measured 1 hour after initiating treatment, and twice a day, throughout hospital stay, ideally pre-nebulization and post-nebulization. Serial peak flow charting gives a good idea of improvement or worsening of the acute attack.[7]

Arterial Blood Gases

Every patient admitted to the ICU for acute severe asthma should have arterial pH and blood gases estimated on admission. Markers of a severe attack are a PaO_2 less than 60 mm Hg, a normal or rising $PaCO_2$ and a respiratory or metabolic acidosis.

Chest Radiography

The usual finding is hyperinflated lungs. The chest X-ray may on occasion show an unexpected pneumothorax or pneumomediastinum. A complicating consolidation or collapse secondary to mucus plugging or allergic broncho-pulmonary aspergillosis may also be detected. Coexisting cardiac failure may also be picked up.

Hematology[1]

A leukocytosis with neutrophilia is a pointer to infection as a possible trigger of the asthma attack. A marked eosinophilia may be a pointer to one of the pulmonary eosinophilia syndromes.

Sputum Analysis[1]

Sputum eosinophilia may give the sputum of an asthmatic a purulent appearance. Hence, a Gram stain and culture should be performed if bacterial infection is suspected.

Electrolytes

Up to 10% of hospitalized asthmatics may have hypokalemia, which in turn increases the risk of potentially fatal arrhythmias.[8] The hypokalemia is usually related to beta-agonist and steroid use.

TREATMENT OF AN ACUTE SEVERE ASTHMA ATTACK (BOX 3)

Oxygen

The majority of asthmatics hospitalized for asthma have hypoxemia of varying degrees of severity at the time of admission. Death when it occurs during an acute asthma attack is almost always a consequence of hypoxemia. Oxygen should be started as promptly as possible. Unlike in patients with chronic obstructive pulmonary disease there is little risk of suppression of ventilatory drive, hence oxygen should be given at high flow rates. The oxygen should be well humidified to minimize bronchial irritation and drying of secretions. Since the main cause of hypoxia in asthma is V/Q mismatch, inspired oxygen concentrations of 35–50% are usually adequate and will reverse the hypoxemia. An oximeter is invaluable in detecting the improvement or deterioration in oxygen saturation as the attack evolves, and repeated arterial punctures are often unnecessary.

Box 3: Management of acute severe asthma

- Oxygen: high flow rates, well humidified
- Nebulized beta-agonists: salbutamol or terbutaline 5 mg in 3 mL N saline; repeat every 1–2 hours initially
- Steroids: intravenous hydrocortisone 200 mg 8 hourly initially
- Intravenous beta-agonists: salbutamol infusion10 µg/min or terbutaline infusion 5 µg/min, if nebulized beta-agonists do not give relief
- Aminophylline: loading dose 6 mg/kg body weight in 20 mL of 5% dextrose intravenously over 20 minutes; subsequent infusion 0.6–0.9 mg/kg/hr via an infusion pump
- Ipratropium: nebulized in a dose of 500 µg every 6 hours
- Adrenaline: 0.5 mL of 1:1,000 solution subcutaneously;* repeat to a maximum of 2 mL
- Ventilatory support

Note: Monitor oxygen saturation, peak flow rates.
Always take chest X-ray on admission, or if there is sudden worsening to exclude a pneumothorax.
*Use when nebulization not available and inhaled beta-agonists have failed. Avoid in patient with ischemic heart disease, hypertension; in elderly patients monitor use carefully.

Nebulized Beta-Agonists

Nebulized beta-agonists are the mainstay of treatment of acute severe asthma. By the time, a patient with severe asthma is hospitalized, metered-dose inhalers will be ineffective because the hyperinflated asthmatic will be too breathless to effectively use his inhaler. These limitations may be overcome by the use of the compressor-driven nebulizer, in which drug delivery is less dependent on a coordinated breathing pattern, and the more prolonged period of administration permits delivery of a larger total dose. Nebulized salbutamol or terbutaline in a dose of 5 mg diluted with 2–3 mL of normal saline must be given promptly. The dose can be repeated every hour initially (watching for excessive tachycardia), and then every 2–4 hours once the patient shows a good response. Theoretically, nebulizers driven by air can worsen hypoxemia if they improve ventilation (by reducing bronchospasm) to a lung unit that is not being perfused, hence they should ideally be driven by oxygen mains, or if driven by a compressor, the patient should simultaneously receive supplemental nasal oxygen.

An oxygen cylinder will not suffice to generate the 6–8 L of gas flow necessary to effectively drive most nebulizers.

Intravenous Beta-Agonists[9]

In severe asthma with extensive small airway mucus plugging, nebulized medication may not be able to reach the affected airways. Hence, the addition of intravenous beta-agonists or aminophylline is recommended in all severe asthma attacks. When given by this route, beta-agonists have a rapid onset of action, but have a high rate of adverse effects, especially tremors and tachycardia, and must be carefully monitored. Salbutamol is given as an intravenous infusion at 10 µg/minute, and terbutaline as an infusion at 5 µg/minute.

Steroids[10]

Every patient requiring critical care for acute asthma, should promptly receive systemic steroid therapy. With the realization that asthma is an inflammatory airway disease, the role of steroids in the treatment of acute asthma has been established beyond doubt. Failure to administer systemic corticosteroids has been cited as a preventable risk factor for death, during an exacerbation of asthma.

Though no study has conclusively shown the benefit of any particular type of steroid over the other, or established any particular optimal dose of steroid, the following generalizations can be made—

- Steroids must be administered early, ideally by the patient himself as soon as his peak flow drops below a pre-specified level (usually <50% of best). If this has not been done, they should be administered as soon as the patient is hospitalized, because they take about 6 hours to act. Available data suggests that a clear benefit from corticosteroids is unlikely to be noticed in the first 6 hours of administration, but may become evident after 6–12 hours of the initial dose.
- In the hospitalized asthmatic patient who does not have a very severe attack and is not vomiting, oral prednisolone in a dose of 40–60 mg given promptly and then repeated daily, may be as effective as intravenously administered steroids.
- In the critically ill asthmatic admitted to an ICU, steroids should be given intravenously in an initial dose of 200 mg of hydrocortisone every 6–8 hours.
- There is no evidence that giving much larger doses significantly speeds up or improves the response. There is on the other hand, the real risk of precipitating an acute steroid myopathy if mega-doses are used initially.
- Complications following a short duration, moderately high-dose course of steroids appear to be minimal even when this has to be continued for 7–14 days.

Aminophylline

Intravenous aminophylline should be started in all severely ill asthmatics admitted to the ICU, especially those who have failed to respond to nebulized beta-agonist and steroids alone.

In patients who are not on oral theophylline preparations at the time of admission, a loading dose of 6 mg/kg body weight diluted in 20 mL of 5% dextrose is given slowly intravenously over 20–30 minutes. The loading dose is increased in smokers (x 1.5) and reduced in patients with pneumonia or cardiac failure (x 0.4), and those with severe hypoxia (x 0.8). The loading dose is best omitted in patients on any form of oral theophylline. Following the loading dose, an infusion is set up at a rate of 0.6–0.9 mg/kg/hour ideally by an infusion pump. The plasma concentration of theophylline must be monitored and maintained within the therapeutic range of 10–20 µg/mL. The bronchodilator effect of theophylline increases when the serum concentrations are maintained at the upper end of the therapeutic range. However, adverse effects also increase and are common at serum concentrations greater than 25 µg/mL. These adverse effects include nausea, vomiting, diarrhea, headache, insomnia, hypotension, cardiac arrhythmias, convulsions and death. Unquestionably, some of the deaths from asthma in most asthma death-audits are linked to theophylline toxicity; hence the drug must be used with the utmost caution, monitoring levels whenever facilities to do so exist. A number of disease states (liver disease, cardiac failure, pneumonia and hypoxemia) and drugs (macrolides and most quinolones) affect theophylline clearance and doses need to be adjusted carefully, and blood levels monitored frequently in these settings.

Adrenaline

Subcutaneous adrenaline is a potent bronchodilator but has the potential to cause cardiac toxicity especially in elderly patients and those with hypertension and pre-existing ischemic disease. Many patients with catastrophic asthma are given preloaded syringes which they can self-administer at the first sign of a severe attack. The usual dose is 0.5 mL of a 1:1,000 solution given subcutaneously. It may be cautiously repeated if the patient is being monitored in an ICU, to a maximum of 2 mL. With the availability, and the ready ease with which nebulized beta-agonists can be administered, adrenaline is now much less frequently used.

Hydration

Many asthmatics are dehydrated during an acute attack because of reduced oral intake and excessive sweating. Adequate hydration with oral and intravenous fluids is essential. As mentioned earlier, oxygen must be well humidified. The efficacy of mucolytics and expectorants is unproven and these are best avoided during an acute attack. Therapeutic bronchial lavage via a bronchoscope in patients on ventilators in an attempt to remove thick mucus plugs, can cause significant desaturation and other complications, and cannot be routinely recommended.

Ipratropium Bromide

Nebulized ipratropium bromide in a dose of 500 µg every 6 hours has some bronchodilator effect, though it is not as

potent a bronchodilator as salbutamol. When these two agents are combined there may be an additive bronchodilator effect. An advantage of ipratropium is that unlike nebulized salbutamol it does not cause any tachycardia.

Antibiotics

Routine administration of antibiotics is not recommended. Though infection is a common trigger, such infections are usually viral.

Magnesium Sulfate[11]

Several studies now show convincingly, that 2 g of Magnesium sulfate ($MgSO_4$) in adults given as a 20-minute IV infusion undoubtedly improves pulmonary function when used as an adjunct to standard therapy. Some studies have shown a trend towards female asthmatics and more severe asthmatics responding better to $MgSO_4$. Because it is a safe and cheap form of therapy, it is worth considering in all refractory cases. A recent study looked at the bronchodilating effects of $MgSO_4$ given via the nebulized route and found that a isotonic solution of nebulized $MgSO_4$ was a useful adjuvant to salbutamol in the treatment of severe asthma in adults.

SUBSEQUENT MONITORING

In addition to subjective improvement in symptoms and signs, objective monitoring of peak flow and oxygen saturation is the best way of assessing the progress of an acute asthma attack. Peak flows are recorded and charted throughout the patient's stay in the ICU. In the initial days, they remain low and morning dips are severe. However, as the asthma stabilizes, the amplitude of these variations gradually decreases, and the peak flow gradually approaches the patient's best or predicted normal.

The PaO_2 returns to normal more slowly than the peak flow and one is often surprised to find some degree of hypoxia persisting for several days after the patient seems to have recovered from an acute attack. Serial measurements of oxygen saturation (SaO_2) are much easier than serial arterial blood gas measurements.

Once subjective and objective improvement occurs, treatment can be gradually scaled down. Intravenous aminophylline is stopped and oral theophylline substituted, intravenous steroids are converted to oral steroids, and nebulized beta-agonists can be replaced by metered dose inhalers. This is the ideal opportunity to teach the patient more about asthma, instruct him about correct inhaler techniques, and give him a self-management plan based on home peak flow recordings.

The patient is usually discharged when he is free of symptoms and peak flows have returned to predicted normal or best, without any of the major diurnal swings that characterize persisting bronchial hyper-reactivity. The first few weeks after discharge from hospital following a severe attack are an unstable period and recurrent attacks and rehospitalization are not uncommon.[12] The patient must have clear, written instructions on his discharge card telling him what to do in case of worsening symptoms. Follow-up in the OPD should ideally be within 2 weeks after discharge.

COMPLICATIONS OF ACUTE SEVERE ASTHMA

The complications of asthma can be divided into those due to the disease itself, and those associated with treatment of the disease. In the former category, we include barotrauma, and all its manifestations like subcutaneous emphysema, interstitial emphysema, pneumomediastinum, pneumothorax and pneumoperitoneum. Collapse, usually of the right middle lobe, is another well-known complication. Arrhythmias are well-recognized complications of hypoxia during an acute attack, and of beta-agonists and theophylline. Hypokalemia too can result from asthma-induced respiratory alkalosis, and from beta-agonists and steroids used in the treatment of asthma. The side effects of large doses of steroids are too well known to enumerate. Acute gastrointestinal bleeds and hypokalemia are the two complications most frequently encountered. Two rarer acute side effects are paradoxical bronchoconstriction that has been reported after intravenous hydrocortisone, methyl prednisolone and even inhaled beclomethasone and budesonide, and acute proximal and distal myopathy in patients receiving large doses of intravenous hydrocortisone. Beta-agonists induce tremors, arrhythmias and hypokalemia when given by the intravenous or nebulized route. The side effects of aminophylline and the special complications that may arise as a consequence of mechanical ventilation are discussed further in this chapter.

VENTILATORY SUPPORT IN ACUTE SEVERE ASTHMA (BOX 4)[13]

Despite all the above measures, a small proportion of patients with acute severe asthma (fortunately no more than 1–2% of all hospitalized asthmatics) will continue to deteriorate and eventually require mechanical ventilation. It must be remembered that even in this select group of asthmatics mechanical ventilation is not therapeutic, but only supportive until bronchodilators and steroids take effect.

INDICATIONS FOR COMMENCING VENTILATORY SUPPORT

- Cardiac or respiratory arrest with apnea or near-apnea.
- Deteriorating level of consciousness with inability to protect the airway.
- Increasing respiratory muscle fatigue.
- Cyanosis or worsening hypoxia (PaO_2 <60 mm Hg) despite maximal oxygen concentrations via face mask [i.e. fraction of inspired oxygen (FiO_2) of 60%].
- Hypercapnia with serial arterial blood gas measurements showing a rising $PaCO_2$. It must be stressed that the arterial blood gas values alone should never dictate when

Box 4: Mechanical ventilation in acute severe asthma

I. Indications—
- Cardiorespiratory arrest with apnea or near-apnea
- Deterioration in the level of consciousness
- Increasing respiratory muscle fatigue
- Worsening hypoxemia despite high oxygen concentrations
- Hypercapnia with rising $PaCO_2$ on serial blood gas estimation

II. Settings—
- Low tidal volumes
- Low respiratory rates
- Low minute ventilation (permissive hypercapnia)
- Prolonged expiratory time

III. Guard against—
- Dynamic hyperinflation (see text)
- High airway pressures
- Hypotension
- Pneumothorax

ventilatory support should commence. Each patient should be evaluated individually; the trend of serial blood gases viewed in context with the clinical condition are far more informative than a single blood gas report viewed in isolation.

HAZARDS IN VENTILATING ASTHMATICS

Even before details of ventilatory support in severe asthma are discussed, it would be prudent to point out that mechanical ventilation though unquestionably life-saving is potentially hazardous and can be directly responsible for significant morbidity and mortality. Death rates in ventilated asthmatics vary from 0–38% in different series, and in a recent review of patients ventilated over a 9-year period in an excellent ICU in the USA, at least one major complication occurred in each and every patient with an overall mortality rate of 22%.[14] Clearly this form of treatment is potentially fraught with danger.

The dynamics of the respiratory system in asthmatics are different from that observed in respiratory failure due to other pathologies. There is little doubt that attempting to ventilate patients with asthma in a manner akin to that used for other lung pathologies has contributed to the high morbidity and mortality in asthmatics. Even with conservative tidal volumes of 500 mL, rates of 12–15/minute and inspiration/expiration (I/E) ratios prolonged to 1:3 to allow adequate time for expiration, the high airway resistance in most severe asthmatics results in the generation of peak airway pressures of 50–60 mm Hg, and the potential for gas trapping and dynamic hyperinflation. Dynamic hyperinflation occurs when a machine preset breath is delivered before the previous expiration is complete, so that the volume of elastic equilibrium is not reached before the next inspiration starts. This results in a positive alveolar pressure persisting at the end of expiration, a phenomenon called occult, intrinsic or auto-positive end-expiratory pressure (auto-PEEP). The degree of auto-PEEP is directly proportional to tidal volume, and inversely related to the expiratory cycle length. Dynamic hyperinflation must be assiduously guarded against when ventilating patients with severe asthma. It can be clinically assessed by direct auscultation (making sure expiration is complete before the next breath is delivered), or by placing a measure-tape around the patient's chest at the level of the nipples, and actually noting the increasing chest girth with each breath, if dynamic hyperinflation is occurring. The most accurate method is to actually measure the amount of auto-PEEP by measuring the pressure deflection when the expiratory tubing is clamped off at the end of expiration (end-expiratory occlusion method). This method should be routinely used to assess the severity of dynamic hyperinflation in any ventilated asthmatic. Another monitor of the severity of dynamic hyperinflation is serial measurements of plateau pressure (P plat). Attempts should be made to keep P plat below 30 cm H_2O.

The two major complications encountered during mechanical ventilation are directly linked to dynamic hyperinflation. These are barotrauma, and circulatory depression with hypotension. Branthwaite in a review on mechanical ventilation in acute severe asthma, stresses that "avoiding death from either tension pneumothorax or acute right heart failure remains the cardinal objective" whilst ventilating severe asthmatics.[15] Barotrauma includes not just pneumothorax, but also interstitial emphysema, pneumomediastinum, subcutaneous emphysema, pneumoperitoneum and tension lung cyst. In a series of 21 episodes of mechanical ventilation for acute severe asthma, pneumothorax occurred in 33%, and was associated with decreased survival.[16] Most episodes of pneumothorax occurred in patients with peak airway pressures exceeding 55 mm H_2O. Hypotension occurred in about 25% of patients in this series. It is caused by high mean intrathoracic pressures impairing venous return and resulting in a fall in cardiac output. The problem may be aggravated by hypovolemia, and by the use of drugs like morphine and diazepam that increase venous capacitance. It can be minimized by maintaining adequate intravascular fluid volume and by shortening the inspiratory phase of ventilation. Hypotension that occurs during the course of mechanical ventilation of severe asthma should always be attributed to excess dynamic hyperinflation until proven otherwise. A brief trial of apnea (30–45 seconds) is usually diagnostic: when hypotension is due to excessive dynamic hyperinflation, period of apnea serves to increase venous return and raise the blood pressure. A favorable response to a trial of apnea should lead to a reduction of the respiratory rate, and increased intravenous fluid administration. If on the other hand, a brief trial of apnea and a fluid challenge fail to promptly improve the blood pressure, then a mechanism other than dynamic hyperinflation is likely. The possibilities then include most ominously, a tension pneumothorax or myocardial depression. Other complications include pneumonia,

atelectasis, arrhythmias, sepsis and complications related to airway management.

VENTILATORY STRATEGIES

Intubation[13]

This should be performed deftly and expeditiously by an expert. Intubation of the critically ill asthmatic involves considerable risk. Many patients have increased bronchospasm and laryngeal spasm during attempted intubation, and hence thorough local anesthetic spray of the pharynx and larynx is important. The patient must be pre-oxygenated, and care taken to avoid gastric aspiration. A large diameter endotracheal tube (ideally ≥8 mm) must be used to minimize airway resistance and facilitate suction. Sedation before intubation is obtained with a small intravenous dose of diazepam (5–10 mg), and if paralysis is needed, pancuronium or vecuronium will suffice.

Controlled Hypoventilation in Acute Severe Asthma

In an attempt to counter the problems posed by traditional ventilation in asthma, Darioli and Perret introduced the concept of controlled hypoventilation in 1984.[17] Realizing that high peak airway pressures were to be avoided at any cost, they set a limit of 50 cm H_2O pressure on the peak inspiratory pressure (Ppk), and achieved this by reducing tidal volume, respiratory rate, minute ventilation and inspiratory flows. This deliberate hypoventilation resulted in $PaCO_2$ levels up to 60–70 mm Hg, which were accepted and tolerated by most patients without complication. Arterial pH was maintained with intravenous sodium bicarbonate if necessary. An adequate oxygen saturation was maintained by increasing the FiO_2 as necessary. Using this strategy in 34 episodes of mechanical ventilation in 26 asthmatic patients, all survived. Equally important, there was no barotrauma in any of their patients. Hypotension, though it occurred in 45% of their cases, was usually transient.

Care of the Ventilated Asthmatic

These patients should be kept well sedated with intravenous diazepam, and if necessary paralyzed with pancuronium or vecuronium. Sedatives, like morphine and meperidine, and paralyzing agents, like d-tubocurarine and gallamine, have histamine-releasing properties and are hence best avoided. Any paralyzing agent used must be cautiously administered. Simultaneous administration of pancuronium with aminophylline may cause serious arrhythmias, and simultaneous administration of pancuronium with steroids has been implicated recently in prolonged residual muscle paralysis and weakness.

Adequate hydration is essential and small doses of normal saline may be instilled down the endotracheal tube in an attempt to liquefy viscid bronchial secretions. Suction must be done efficiently with meticulous care taken to ensure full aseptic precautions.

As mentioned earlier, complicating barotrauma, hypotension and dynamic hyperinflation must be guarded against by frequent checks of auto-PEEP.

Weaning[13]

Most patients do not require prolonged periods of ventilatory support, and once bronchospasm has settled and the asthma attack is felt to have resolved on clinical grounds, weaning may be attempted. Most patients can be easily and successfully weaned. Some units prefer to switch to the pressure support ventilatory mode during the weaning process. Difficulty in weaning may be encountered in patients with respiratory muscle weakness from hypokalemia, hypophosphatemia, excessive use of steroids, and long-term use of neuromuscular blocking drugs.

Unconventional Therapies

Many anecdotal case studies have reported on the use of various anesthetic agents, both intravenous and by inhalation, in the therapy of refractory bronchospasm in the ventilated asthmatic. The drugs used include halothane, ether, isoflurane, enflurane, thiopental, ketamine and droperidol. Heliox (an oxygen-helium mixture) has been tried in eight randomised trials to date, and in the occasional patient with acute severe asthma or brittle asthma can result in dramatic improvement.[18] There have also been reports of extracorporeal membrane oxygenation (ECMO) succeeding when all conventional forms of therapy have failed.

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CHAPTER 34

Community-Acquired Pneumonias Requiring Critical Care

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INTRODUCTION

Pneumonias can be classified into community-acquired pneumonias (CAP), nosocomial pneumonias, pneumonias occurring in the immunocompromised host and aspiration pneumonias. This chapter deals with CAP requiring critical care.[1]

Community-acquired pneumonias are an important cause for hospital admissions. Most pneumonias are managed in the general wards of the hospital. Critical care for CAP may however be necessary under the following circumstances (Box 1)—

- When pneumonia occurs in the very young and the old.
- When it is complicated by acute respiratory failure or shock.
- When a CAP leads to the acute respiratory distress syndrome (ARDS).
- When pneumonia in rare instances is complicated by spread of infection to other organs or systems, notably the pericardium, meninges or the brain.
- When it exists as a complication of another serious illness for which the patient is hospitalized, e.g. a cerebrovascular accident, diabetic ketosis or head injury.
- When it is the result of a fulminant viral or bacterial infection. Fulminant influenzal pneumonia can cause death within 48 hours. Fulminant bacterial infections due to virulent strains of the *pneumococcus*, *Haemophilus influenzae*, or Gram-negative bacilli carry a forbidding mortality in spite of good care and appropriate management. Infections by rare virulent organisms like *Yersinia pestis* and anthrax can cause fulminant infections and quick death. The tubercle bacillus on occasion can cause extensive acute consolidation resulting in a life-threatening illness; the diagnosis is missed if this possibility is not kept in mind.
- When community-acquired pneumonia occurs in an immunocompromised host as in a patient with leukemia, malignancy or acquired immune deficiency syndrome (AIDS), or in a patient who has recently received radiation or is on corticosteroids or cytotoxic drugs.

Box 1: Indications for critical care in community-acquired pneumonia

- At extremes of age
- When complicated by acute respiratory failure or shock
- When followed by ARDS
- When complicated by spread of infection to other organs or systems, e.g. the brain, meninges or pericardium
- When pneumonia occurs as a complication of another serious illness, e.g. head injury, cerebrovascular accident
- When the etiology is a fulminant viral or bacterial infection
- When it occurs in an immunocompromised host

Abbreviation: ARDS, acute respiratory distress syndrome.

ETIOLOGY

There is a paucity of data on the etiology of CAP from developing countries in general and India in particular. The high cost of routinely performing microbiological and serological tests in all patients with CAP is probably the main reason for this. Moreover, the cost effectiveness of making such an exact microbiological diagnosis of CAP remains debatable even in the West. Empirical antibiotics, started promptly, according to guidelines would be the preferred approach, but guidelines

from the West cannot be blindly transposed to India without some idea of local epidemiology. A recent prospective study of 100 adult patients hospitalized in two major Mumbai hospitals was the first attempt to determine the etiology of CAP in this country.[2] Despite an array of costly laboratory tests being performed, no organism could be detected in 42% of patients. 23% of patients had *Streptococcus pneumoniae* isolated, whilst 'atypicals' accounted for 19% of cases (*Chlamydia* 11%, *Mycoplasma* 5% and *Legionella* 3%). *H. influenzae* and *Moraxella cattarrhalis* accounted for 9% and 6% of cases respectively, whilst Gram-negatives accounted for only 5% of all cases. These findings and the overall ranking of pathogens are remarkably similar to data from most Western series.[3]

Community-acquired pneumonias occurring against a background of chronic lung disease can produce critical illnesses and often precipitate respiratory failure. Acute on chronic respiratory failure is most frequently observed when acute pneumonia occurs in a patient with chronic bronchitis or in a patient with bronchiectasis. Pneumonia in these patients is most often due to the *Pneumococcus*, *H. influenzae*, or to Gram-negative organisms.[4]

RECENTLY DESCRIBED VIRAL PNEUMONIAS

Severe Acute Respiratory Syndrome

Severe acute respiratory syndrome (SARS) is a viral respiratory illness (incubation period 2–4 days) caused by the corona virus. It was first reported in Asia in 2003 and over the next few months spread to North and South America, Europe and Asia (including India) before it was contained. Of a total of 8,098 people infected, 774 of them died. The spread was by close person to person contact through droplet infection. The symptoms are common with other respiratory viral infections—high fever, headache, bodyache, breathlessness, cough. Pneumonia involving one or both lungs and ARDS were observed in severe cases. The mortality as mentioned above was high in patients who developed pneumonia and ARDS. Critical care and the need for ventilator support were necessary in these severely ill patients.

The Middle Eastern Respiratory Syndrome—Corona Virus

The Middle Eastern Respiratory Syndrome—Corona Virus (MERS—CoV) was reported by the World Health Organization (WHO). The outbreak arose in the eastern province of Saudi Arabia, a total of 23 cases being reported between April and May 2012. It has been reported from other countries in the Middle East but yet there is no confirmed report of this respiratory viral infection in India. The spread is by close person to person contact, spread being through droplet infection.

The infection (which has an incubation period for 2–10 days) ranges from mild to fulminant, the clinical syndrome being very similar to SARS. An initial phase of non-specific fever, non-productive cough and occasional diarrhea lasting for several days may progress to a fulminant pneumonia requiring critical care and ventilator support. Radiological findings in patients with pneumonia show unilateral or bilateral infiltrates and in the very severe cases diffuse reticulonodular shadows. There was a 65% case mortality in this outbreak. This is of great concern, as there is a definite risk of this viral infection having a larger spread in the years to come.

PATHOGENESIS[5]

This varies with the infecting organism. Aspiration of organisms resident in the nasopharynx is responsible for *Pneumococcal pneumonia*, as also for pneumonia caused by other Gram-positive and Gram-negative organisms. Viral infections are generally due to inhalation of infected droplets from other patients. Inhalation of water droplets contaminated with Legionella produce a Legionella infection. Hematogenous infection from a distant source of sepsis can also produce pneumonia. *Staphylococcal pneumonias* and Gram-negative pneumonias are occasionally caused by hematogenous infection.

CLINICAL FEATURES[6]

Fever, prostration, respiratory distress, cough with signs of consolidation over a lobe and a polymorphonuclear leukocytosis are the classic features of pneumonia. Signs of consolidation include an impaired percussion note, bronchial breathing and respiratory crackles over the involved lobe. None of these signs may be evident, if the pneumonia is close to the hilum or is centrally placed within a lobe. Inspiratory crackles localized to a lobe should be looked out for carefully in a suspected case. This may be the only physical finding in the chest in a fulminant pneumonia. An X-ray chest is of course diagnostic. The shadow produced by a consolidation may not be always evident in the very early stage of the natural history of pneumonia. The British Thoracic Society in 1987 identified three core features that could easily be checked at admission and which were of great prognostic value.[7] They were—

- Respiratory rate greater than 30/minute.
- Diastolic blood pressure (BP) less than 60 mm Hg.
- Blood urea greater than 7 mmoL/L.

Patients with two or more of these core features had a 21 times higher risk of death. Besides, this simple bedside rule had a sensitivity of 88%, specificity of 79% and a high negative predictive value of 99%. Other features of grave prognostic import were mental confusion or obtundation, hypoxia (PaO_2 <55 mm Hg) and the presence of metabolic acidosis (pH <7.2). Pointers to the severity of pneumonia are listed in Box 2.

There are a few important variations in the clinical picture described above (Box 3).

- In some pneumonias, non-respiratory symptoms predominate and confuse the picture. A lower lobe pneumonia may present with acute abdominal pain and may mimic an acute abdomen. A wrong diagnosis of acute appendicitis

Box 2: Pointers to severity of community-acquired pneumonia

- Age >60 years
- Associated with pre-existing serious illness
- Respiratory rate >30/min
- Systolic blood pressure <80–90 mm Hg
- Mental confusion
- WBC count <4000/mm^3
- PaO_2 <55 mm Hg on oxygen; $PaCO_2$ >48–50 mm Hg
- Metabolic acidosis pH <7.2
- Chest X-ray shows multilobe or spreading shadows
- Spread of infection to pericardium or meninges
- Multiple organ dysfunction syndrome present

Box 3: Unusual presentations of acute life-threatening community-acquired pneumonias

- Predominance of non-respiratory symptoms, e.g. acute abdominal pain in case of lower lobe pneumonia
- Subtle manifestations (tachycardia, increased respiratory rate, mental confusion, rapid clinical deterioration) seen sometimes in old, debilitated patients
- Acute delirium, confusion, disorientation
- Multisystem involvement (hepatitis, diarrhea, hypotension, SIADH, renal involvement) mainly in *Legionella pneumonia*; can also occur in other pneumonias
- Atypical manifestations in *Mycoplasma pneumonia*
- Acute respiratory distress, inspiratory crackles similar to the acute form of interstitial pulmonary fibrosis, bilateral pulmonary shadows, with rapid progression to acute respiratory failure, is a rare manifestation of tuberculous pneumonia

Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone.

or acute hepatitis is frequently made, particularly in children and young adults.

- Life-threatening CAP in old debilitated patients may present with subtle manifestations. Tachycardia, an increased respiratory rate, mental confusion, and a rapid deterioration in the clinical state leading to death may be observed.[8]
- Acute delirium, with confusion and disorientation may occur with any acute pneumonia. It especially occurs with Legionella infection. Multisystem involvement can occur with any pneumonia but again is often present early with acute Legionella infection. Hepatitis, diarrhea, hyponatremia, syndrome of inappropriate antidiuretic hormone (SIADH), and renal involvement occurring in a patient with consolidation should suggest the diagnosis of a Legionella infection.[9]
- The commonest atypical pneumonia is probably a mycoplasmal infection. Acute myocoplasmal infection (like Legionella infection) can also rarely cause multisystem involvement. Cold agglutinins are positive in about 50% of patients with mycoplasmal pneumonia.[10]
- Acute tuberculous pneumonia can present with bizarre manifestations. An unusual presentation is that of acute respiratory distress, bilateral shadows in the lungs with inspiratory crackles indistinguishable from those seen in interstitial pulmonary fibrosis (Fig. 1). There is cough but no sputum for examination. The patient can progress to quick acute respiratory failure with a low PaO_2 (<60 mm Hg), even on supplemental oxygen. The diagnosis is impossible without an examination of bronchoalveolar lavage samples, which show acid fast bacilli, or without a transbronchial and in rare instances, an open lung biopsy. The biopsy shows tubercles on histopathological examination, and acid fast bacilli on appropriate staining of tissue sections.

COMPLICATIONS (BOX 4)

The most important complication is acute respiratory failure. There is often a large shunt from right to left in pneumonia, particularly when more than one lobe is involved. This leads to a marked fall in the PaO_2 even when the patient is on oxygen at 4–6 L/minute. Acute respiratory failure can also occur because of the evolution of the acute respiratory distress syndrome following upon a fulminant lobar pneumonia (Fig. 2). Multiple shadows in both lungs, with a large right to left shunt following a lobar consolidation, is now invariably thought to be due to acute lung injury, ARDS, and not to spreading infection in the lungs.

Acute life-threatening pneumonia is a source of sepsis.[11] All the complications of the sepsis syndrome may be observed. These include hypotension, septic shock and tissue hypoperfusion with metabolic acidosis culminating in multiple organ failure.

Spread of infection to contiguous areas, or hematogenous spread, may rarely add to the gravity of the illness. Empyema is the commonest of these complications. It may be tucked away posteriorly in the paravertebral gutter and can be missed on a chest X-ray. It is clearly demonstrated on a computed tomography (CT) of the chest. It may be responsible for the sepsis syndrome after the consolidation in the lung has resolved clinically and radiologically.

Acute purulent pericarditis is now a very rare complication. It is lethal, if undiagnosed and not promptly treated. As little as 300 mL of pus in the pericardium can cause death from cardiac tamponade in a child. The diagnosis should be suspected when there is a sudden clinical deterioration in a patient with acute pneumonia, particularly in the presence of shock with a raised central venous pressure.

Acute pyogenic meningitis may be the presenting feature of an underlying lobar pneumonia. Neck stiffness and a positive Kernig's sign may however be present in acute lobar pneumonia even without acute meningitis. This is more frequently observed with upper lobe pneumonia in young adults. A lumbar puncture is always mandatory as it is the only certain way of distinguishing meningism from meningitis.

Fig. 1: *Legionella pneumonia*—This patient presented with high-grade fever , chest pain and cough. Chest X-ray showed diffuse fluffy opacities seen in both lung fields suggestive of legionella pneumonia. Legionella antigen was detected on urine examination

Fig. 2: *Mycoplasma pneumonia*. A 47-year-old male patient presented with fever and cough, white blood cells (WBC) count was normal. Anti-mycoplasma titers were very high. Chest X-ray demonstrates streaky and conglomerated opacities in both lower zones, more so on the left side representing *Mycoplasma pneumoniae*

Box 4: Complications of acute life-threatening community-acquired pneumonia

- Acute respiratory failure
- Acute lung injury (ARDS)
- Sepsis syndrome or MODS
- Acute circulatory failure
- Spread of infection to contiguous areas or hematogenous spread, e.g. empyema, acute meningitis, cerebral abscess, acute pericarditis
- Acute left ventricular failure/acute myocarditis
- Acute abdominal distension, acute dilatation of the stomach, ileus
- Femoral vein thrombosis

Abbreviations: ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome.

A sharp deterioration in the clinical state with confusion, delirium and severe prostration may also occur when infection from the lungs spreads hematogenously to produce one or more cerebral abscesses. Localizing signs may be present. A CT Scan is invaluable in confirming the clinical diagnosis.

Acute left ventricular failure is a rare complication in patients with pre-existing left ventricular disease. Acute myocarditis can and does however occur in some patients with acute influenza. It is characterized by tachycardia, hypotension, cardiac dilatation and a diastolic gallop. It may progress to an increasingly severe low output state and death from cardiogenic shock.

In the older age group, patients with acute pneumonia may present with marked abdominal distension. Acute dilatation of the stomach is particularly dangerous, as it compounds respiratory difficulties. Ileus may also occur due to toxemia.

Femoral vein thrombosis is occasionally observed in patients critically ill with pneumonia. Sudden death in acute pneumonia could well be related to pulmonary embolism.

DIFFERENTIAL DIAGNOSIS[12]

A large pulmonary infarct is an important differential diagnosis of acute lobar pneumonia. The distinction at times in difficult. Acute extrinsic allergic alveolitis may present with bilateral upper lobe shadows, whilst acute cryptogenic fibrosing alveolitis may produce bilateral lower lobe shadows with increasing hypoxia. Acute eosinophilic pneumonia should be suspected on the fairly typical radiological features (peripheral shadows in both lung fields). Acute consolidation due to a vasculitis (e.g. Wegener's) may be indistinguishable from consolidation due to an infection. Finally an acute life-threatening pneumonia may occur as a presenting feature of bronchial obstruction produced by a tumor or a foreign body. Aspiration of betel nut (supari) can cause a life-threatening acute necrotizing pneumonia.

Investigations[1]

The diagnosis is made on the basis of clinical features and an X-ray of the chest, which shows one or more areas of consolidation.

Radiological Abnormalities[1]

Generally speaking, it is impossible to determine the etiology from the nature of the radiological shadowing. Homogenous shadows, lobar or segmental in distribution, are more often seen in bacterial pneumonias. Diffuse patchy shadows occur more frequently in atypical pneumonias (e.g. mycoplasmal or viral pneumonias). The latter however also can produce homogenous shadows indistinguishable from bacterial pneumonia. The development of ARDS is recognized by bilateral fluffy shadows, with increasing hypoxia.

Hilar adenopathy is often observed particularly in children and young adults with tuberculous pneumonia. Rarely, it may also occur with mycoplasmal infection.

Pleural effusion is common and when present, a diagnostic tap is helpful in determining the causative organism responsible for pneumonia.

Microbiological Tests[1]

The nature of the infecting organism can only be determined by specific microbiological tests. Sputum samples should be quickly collected whenever possible, but antibiotic therapy should be started without awaiting results. Blood cultures are also sent prior to starting treatment. A positive blood culture is rare in our set-up, but when present, identifies the pathogen with certainty.

Sputum examination in our opinion has a low sensitivity but a high specificity, if positive. A Gram stain and a culture should be done. It is important to first ascertain the adequacy of the sample. If under low power, the sputum sample shows more than 25 neutrophils and less than 10 epithelial cells, it signifies a satisfactory sample, which is worth staining and worth culturing. Such a specimen is minimally contaminated by oropharyngeal flora. The presence of just one kind of organism in large numbers on Gram stain of a suitable sputum specimen is very significant. This finding provides a good guide for initial antibiotic therapy.

Positive sputum cultures should not be viewed as sacrosanct in arriving at an etiological diagnosis. The culture may not necessarily reflect the etiology of infection deep within the lung. Washing or diluting the sputum may help by encouraging only bacteria present in large numbers to grow on culture. We feel that if repeated cultures grow the same organism, the results are generally significant. Sputum cultures are generally negative, or may only grow commensals if the patient has received an antibiotic before admission to the ICU. Most patients have received one or more courses of antibiotics in the community before their eventual hospitalization.

If pleural fluid is present, it should be aspirated, and sent to the laboratory for Gram stain and culture. Organisms seen on Gram stain, or grown on culture of the pleural fluid point to the etiological agent responsible for pneumonia.

A positive diagnosis of pneumococcal pneumonia can be made more frequently by testing for pneumococcal polysaccharide capsular antigen in sputum, blood, urine and pleural fluid, by counter immunoelectrophoresis, co-agglutination and latex agglutination.

The diagnosis of acute viral, mycoplasmal, other atypical pneumonias and Legionella infection is made by serological methods which identify antibodies in the blood at the start of the illness, and again 10–14 days later. The presence of legionella antigen in the urine allows an early diagnosis. There generally has to be a fourfold rise of the antibody titer against a particular organism for the test to be considered as positive. This is obviously of no use in the management of life-threatening infections by these agents. Specific IgM antibody detection can however aid early diagnosis of Legionella or mycoplasmal infection. It is unfortunate that these tests are unavailable except in a few microbiological laboratories in this country. The cost of some of these specialized serological tests is also high and a deterrent to routine use of these tests.

In patients who are seriously ill, who have not responded to initial therapy, and in whom an etiological diagnosis is therefore important for management, secretions from the lower respiratory tract should be obtained through fiberoptic bronchoscopy using protected brushes,[13] and through bronchoalveolar lavage.[13] Material obtained by these methods should be appropriately stained and cultured, and subjected, if necessary to special tests stated above.

A CT- guided biopsy of the area of lung consolidation may also be necessary to arrive at a diagnosis. In difficult cases, one may have to resort to open lung biopsy. This is particularly necessary in life-threatening acute respiratory infections which have not responded to an empiric regime of antibiotics. Through open lung biopsy, we have stumbled occosionally on bizarre manifestations of acute pulmonary tuberculosis and acute vasculitis, conditions which require a different approach in management.

The diagnostic value of the various investigations done for CAP is listed in Table 1.

General Investigations

Leukocytosis greater than 15,000/mm^3 is generally present in bacterial infections. In patients with atypical pneumonias due to viral or mycoplasmal infections, the white blood cell count is usually normal. Severe leukocytosis (WBC >30,000/mm^3) or marked leukopenia (WBC <4,000/mm^3) is a poor prognostic sign.

The PaO_2 is often low and in severe cases may be less than 50 mm Hg, even when the patient is receiving oxygen at a flow rate of 6–10 L/minute. Hypocapnia is usual and this results in respiratory alkalosis. In critically ill patients, overall alveolar hypoventilation ultimately prevails, and the $PaCO_2$ shows a progressive rise. A sudden deterioration in the clinical state is characterized by increasing hypoxia, hypercapnia, and a combination of respiratory-cum-metabolic acidosis.

Abnormal liver functions are frequently present, particularly a mildly raised serum transaminase and slightly elevated serum bilirubin. Hypokalemia and hypoalbuminemia

Table 1: Diagnostic value of investigations in community-acquired pneumonia

Tests	*Remarks*
Microbiological Sputum Gram stain/culture	• Check if sample satisfactory • Collect sputum prior to starting antibiotics • Oropharyngeal contamination may be present • Low specificity (10%), high sensitivity (70–80%), if positive • Washing/diluting sample helpful
Blood culture	• Should be done prior to starting antibiotics • Positive cultures rare in our set-up, but when present, identifies the pathogen
Pleural fluid Gram stain/culture	• If positive, useful in establishing etiological agent
Serological *Antigen detection:* Pneumococcal (blood, urine) Legionella (urine) Cold agglutinins	 • Mainly useful for pneumococcal infection • Accurate means of diagnosing Legionella infection • Positive in over 50% of patients with mycoplasmal pneumonia
Antibody detection: Anti-mycoplasma Anti-chlamydia Anti-influenza	 • Helps in diagnosis of mycoplasma, chlamydia, and viral pneumonia
Invasive tests: Examination of secretions obtained from protected brush biopsies, bronchoalveolar lavage (BAL), or CT guided or transbronchial biopsy of lesion Open lung biopsy	• Should be done in serious illness not responding to initial empiric antibiotic therapy • Helps in etiological diagnosis • Helps in diagnosis in the above situation if BAL, protected brush smears and CT guided biopsies are negative

Abbreviation: CT, computed tomography.

may be observed. Inappropriate secretion of the antidiuretic hormone may cause well-marked hyponatremia. This is more commonly observed in Legionella infections, but can also occur with other pneumonias.

A raised blood urea, proteinuria and hematuria may also occur. Investigations in critically ill patients should include an assessment of the function of various organ systems.

MANAGEMENT

Use of Antibiotics (See Table 1 of Chapter 46)[1,14]

Antibiotics must be started promptly, empirically, and by the parental route in all hospitalized patients with CAP. If possible sputum and blood culture should be sent off prior to initiating therapy. The *pneumococcus* must always be covered as must *H. influenzae* and atypical bacteria. Antibiotic choice must be governed by knowledge of local epidemiology and resistance patterns. More epidemiological studies from different parts of the country will help physicians to empirically but accurately choose their initial antibiotic regime. The following are the author's antibiotic recommendations based on the results of an epidemiological study from Mumbai.[4]

- *If the patient is ill but not in the ICU* We would recommend co-amoxyclav or ceftriaxone in full intravenous doses plus either a quinolone or a macrolide intravenously. This combination would effectively cover the *pneumococcus*, *H. influenzae*, *M. catarrhalis*, *mycoplasma*, *chlamydiae* and *legionella*.
- *If the patient fails to respond or is ill enough to be in the ICU* We would in addition add on an antibiotic with Gram-negative (specifically anti-pseudomonal) cover. In the Mumbai series, though Gram-negatives were rarely responsible for CAP (5% overall), there numbers rose in ICU patients (*Pseudomonas*, 2 out of 19, *Klebsiella*, 2 out of 19). An anti-pseudomonal antibiotic like ceftazidime or ticarcillin should be considered in this critically ill group of patients, where failing to cover a Gram-negative pathogen could make the difference between life and death.
- *Specific situations* If staphylococcal infection is strongly suspected on clinical or radiological grounds, intravenous cloxacillin can be added. If there is a strong suspicion of methicillin-resistant *Staphylococcus aureus* (MRSA),[15] vancomycin should be added. If the history suggests aspiration is a possibility, metronidazole should be used.

If over 48 hours, the patient has not improved, and if sputum is unavailable for examination, or is non-contributory to the diagnosis, it is important to make an exact etiological diagnosis.[13] Examination of bronchoalveolar lavage material, or of material obtained by protected brush biopsy through a fiberoptic bronchoscope may help. In desperate situations, a CT-guided biopsy or an open lung biopsy may be necessary. It is important to be bold and establish an early diagnosis in patients who are critically ill and who do not respond to a wide cover of multiple antibiotics. Yet boldness must be tempered with good sense. The decision as to whether a patient will stand an invasive diagnostic procedure, and whether he is likely to benefit from it or not, is a matter of judgment based on experience and expertise.

Management in the ICU[16]

The patient in the ICU should be carefully monitored with regard to his vital signs and his oxygen saturation. An

increasing respiratory rate, a falling blood pressure, and increasing hypoxia in spite of oxygen therapy, are warning signs of impending cardiorespiratory failure. We use ventilatory support if the respiratory rate is greater than 36–40/minute, if there are signs of respiratory muscle fatigue, if the PaO_2 is less than 55 mm Hg on oxygen, or if the $PaCO_2$ is greater than 50 mm Hg. We also use ventilator support in the presence of circulatory failure as evinced by hypotension, metabolic acidosis and other features of a low output state. Nearly 58–85% of patients with severe CAP require ventilatory assistance. There may be special ventilatory needs in severe CAP, particularly if extensive unilateral involvement is present. Patient positioning may be a simple and effective way of improving oxygenation if unilateral lobar pneumonia is present. By positioning the pneumonic lung up and the non-involved lung down, gravity can increase perfusion to the dependent non-involved lung, optimizing matching between ventilation and perfusion and thus improving oxygenation.[17] We generally initiate ventilator support in the volume control mode. If however peak inflation pressures are high, we prefer the pressure control mode using a pressure control limit of not greater than 30 cm H_2O. Positive end expiratory pressure (PEEP) is adjusted to optimize oxygenation. Sedation and rarely induced muscle paralysis may be necessary for efficient ventilator support.

Noninvasive ventilation has been tried but with limited success in this critically ill group of patients but if the patient continues to deteriorate despite a short trial, intubation and mechanical ventilation should not be delayed. Patients may require ventilatory support for several weeks.

Fluid and electrolyte balance should be carefully maintained, and support to multiple organ systems is often necessary in fulminant infections. Inotropic support and/or vasopressor support need to be used in patients who are hypotensive.

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CHAPTER 35

Massive Hemoptysis

INTRODUCTION

Hemoptysis is the expectoration of blood, the source of bleeding being below the vocal cords, either from the tracheobronchial tree or the lungs. In most cases, hemoptysis though frightening to the patient is self-limiting, and requires no treatment other than sedation and rest. In a few instances, hemoptysis may be massive and life-threatening, and requires intensive care and emergency management. There is no generally accepted definition as to what constitutes massive hemoptysis. Various reports in literature use different criteria—hemoptysis varying in range from 100 mL/24 hours to 1,000 mL over a period of several days.[1-3] Most critical care units would consider the loss of 600 mL or more of coughed blood in 24 hours to constitute massive hemoptysis. From the practical point of view, hemoptysis should be considered massive when it is life-threatening. This can be due to exsanguination, or to the risk of asphyxiation following aspiration or retention of blood within the lungs. Thus, the risk of death from hemoptysis has been shown to be related to the amount of blood expectorated, the rate of bleeding, the quantity of blood retained within the lungs, and the underlying pulmonary reserve, regardless of the etiology of bleeding.[2-4] The rate of bleeding is of crucial importance. Crocco and coworkers,[5] in a classic study in 1968 showed that hemoptysis of 600 mL blood in less than 4 hours was associated with a mortality of 71%, compared to 22%, if the same blood loss was within 4–16 hours and 5% if this loss occurred from 16 to 48 hours.

BLOOD SUPPLY TO THE LUNGS

The lungs have two relatively independent sources of blood supply: (1) the pulmonary circulation and (2) the bronchial circulation, so that bleeding with resultant hemoptysis can occur from either of these two vascular beds, or from both.

The pulmonary circulation arising from the right ventricle and the pulmonary artery is a low pressure, high-volume conduit which arborizes into fine capillaries around the alveoli, mediating gas exchange.

The bronchial circulation is a part of the systemic vascular bed and serves as a nutritional source for the structural elements of the lung. There are usually one or two bronchial arteries per lung, arising from the aorta and less commonly from the intercostal arteries. In a small percentage of individuals, the anterior spinal artery originates from the bronchial artery. The bronchial circulation has a systemic blood pressure, and factors which regulate and control systemic arterial flow and pressure, will equally influence blood flow and blood pressure within the bronchial vessels. The bronchial vessels anastomose freely with each other in the peribronchial space, and also penetrate the bronchial wall to form an extensive submucous plexus.

Beyond the terminal bronchioles, the bronchial vessels anastomose quite extensively with the precapillary pulmonary arterioles and the pulmonary veins. This anastomosis is often exaggerated in some lung pathologies, as for example in bronchiectasis, and plays an important role in severe bleeding that occasionally occurs in diseased lungs. The bronchial arteries also become hyperplastic and tortuous in many conditions causing hemoptysis. As these arteries are associated with the airways and are under systemic pressure, they have a propensity to bleed profusely in diseases involving the airways. Generally speaking, bleeding (and hemoptysis) due to erosion or rupture of bronchial vessels is brisker and more profuse, compared to bleeding due to erosion or rupture of pulmonary vessels.

Box 1: Important causes of life-threatening hemoptysis

- Tuberculosis can cause massive hemoptysis due to several mechanisms—
  - Bronchial ulceration with necrosis and rupture of underlying bronchial vessels, or rupture of pulmonary vessels due to alveolar necrosis in tuberculous pneumonia
  - Rupture of aneurysmal portion of a branch of the pulmonary artery (Rasmussen's aneurysm) in cavitative tuberculosis
  - Erosion of bronchial arteries by pressure of a calcified hilar lymph node on a bronchus
  - Due to bronchiectasis occurring as a sequel to tuberculosis
  - Formation of a mycetoma in chronic tuberculous cavities
- Bronchiectasis
- Lung abscess
- Mitral stenosis
- Mycetomas
- Cystic fibrosis and in severe pneumonia as in human immunodeficiency virus (HIV) infection
- Bronchogenic carcinoma or other tumors
- *Iatrogenic hemoptysis:* Following bronchoscopy, Swan-Ganz catheterization or transthoracic needle biopsy, tracheo-arterial fistula and malposition of chest tube
- *Intra-alveolar hemorrhage:* Autoimmune disorders, pulmonary vasculitis, Wegener's granulomatosis, Goodpasture's syndrome, bleeding disorders
- *Vascular anomalies:* Arteriovenous malformations
- Trauma to the chest
- Cryptogenic hemoptysis

This chapter now considers the common causes, clinical features, approach to diagnosis and management of life-threatening hemoptysis.

IMPORTANT CAUSES OF LIFE-THREATENING HEMOPTYSIS (BOX 1)[4,6]

Tuberculosis

Tuberculosis still remains the most important and most frequent cause of massive hemoptysis in India and other developing countries. Hemoptysis may occur in active tuberculous infection of the lung, or may be a sequel to burnt-out disease. Most patients with active tuberculosis, who have severe hemoptysis, have cavitative lung disease with acid-fast bacilli present in the sputum. There are several mechanisms of massive hemoptysis in tuberculosis. These include—

- Bronchiolar ulceration with necrosis and rupture of the underlying bronchial vessels in tuberculous pneumonia. Rupture of pulmonary capillaries due to alveolar necrosis may also be an associated feature.
- Rupture of an aneurysmal portion of a branch of the pulmonary artery in cavitative tuberculosis. Rupture of a Rasmussen aneurysm[7] is a well-accepted cause of massive hemoptysis in either active tuberculosis, or in patients with prior infection. Pulmonary arteries traversing thick-walled cavities develop aneurysmal dilatations due to local inflammation of the vessel wall. These aneurysms herniate and project into the cavity lumen. Sudden transient increase in pulmonary artery pressure, or continued inflammation of the vessel wall can cause rupture of the aneurysm with profuse hemorrhage and hemoptysis.
- A healed calcified lymph node at or near the hilum can press on a bronchus, and erode through a bronchial vessel into the lumen of the airway, resulting in massive hemoptysis. The patient may cough up this calcified node in the form of a broncholith. This may immediately precede hemoptysis, or occur during a bout of hemoptysis.
- Massive hemoptysis can occur due to bronchiectasis which often occurs as a sequel to tuberculosis. Bleeding occurs due to erosion of tortuous, enlarged bronchial vessels, and a profuse anastomosis between the bronchial and pulmonary circulation.
- Chronic tuberculous cavities often predispose to the formation of aspergillomas. The latter can cause profuse bleeding.

Bronchiectasis

Bronchiectasis is often associated with bronchial artery hypertrophy, expansion of the peribronchial and submucosal bronchial arterial network, and increased anastomosis between the bronchial and pulmonary circulations. Massive bleeding can originate from hypertrophied bronchial arteries (under high systemic pressure), or from the submucosal vascular plexus in the bronchiectatic segments.

Mitral Stenosis

Before the era of valvulotomy and mitral valve replacement, massive hemoptysis occurred in 9–18% of patients with mitral stenosis.[5] Severe hemoptysis is generally due to rupture of engorged, tortuous, dilated varicose bronchial veins that result as a consequence of an elevated left atrial pressure and passive pulmonary hypertension. In these patients, massive hemoptysis may be precipitated by respiratory infection, by a bout of coughing, or by an increase in intravascular volume, as in pregnancy.

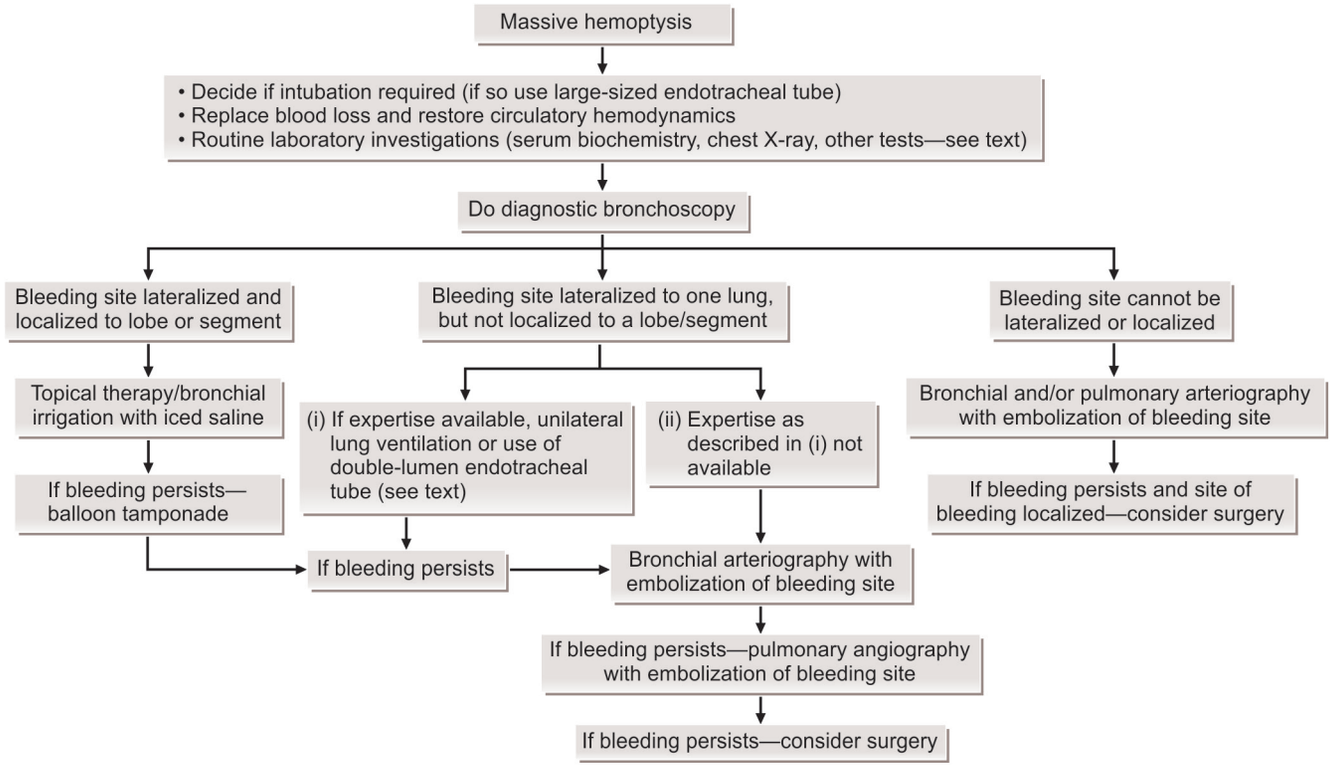
Lung Abscess

Masssive bleeding occurs in 20–50% of lung abscess patients with hemoptysis. It is related to necrotizing inflammation of the lung parenchyma eroding bronchial and pulmonary vessels.

Mycetomas

Mycetomas are fungal balls occurring in patients with pre-existing cavitary lung disease. They are most frequently seen in tuberculous cavities, but have been reported in cavitary disease secondary to sarcoidosis, lung abscess, cavitary carcinoma, bronchiectasis, bullous emphysema and

Flowchart 1: Algorithm for the management of massive hemoptysis


Massive hemoptysis
• Decide if intubation required (if so use large-sized endotracheal tube)
• Replace blood loss and restore circulatory hemodynamics
• Routine laboratory investigations (serum biochemistry, chest X-ray, other tests—see text)
Do diagnostic bronchoscopy
Bleeding site lateralized and localized to lobe or segment
Bleeding site lateralized to one lung, but not localized to a lobe/segment
Bleeding site cannot be lateralized or localized
Topical therapy/bronchial irrigation with iced saline
If bleeding persists—balloon tamponade
(i) If expertise available, unilateral lung ventilation or use of double-lumen endotracheal tube (see text)
(ii) Expertise as described in (i) not available
Bronchial and/or pulmonary arteriography with embolization of bleeding site
If bleeding persists and site of bleeding localized—consider surgery
If bleeding persists
Bronchial arteriography with embolization of bleeding site
If bleeding persists—pulmonary angiography with embolization of bleeding site
If bleeding persists—consider surgery

pulmonary infarction. The most frequent mycetoma is an aspergilloma. The cause of massive bleeding in a mycetoma is disputed. Vascular injury by aspergillus-associated endotoxin, aspergillus-related proteolytic activity and a Type III related hypersensitivity reaction have all been postulated.[8]

Bronchogenic Carcinoma and Other Tumors

These rarely cause massive or life-threatening hemoptysis.

Iatrogenic Hemoptysis

This is a potential complication of bronchoscopy, transthoracic needle biopsy, or the use of a Swan-Ganz catheter.

Rupture of the pulmonary artery is the most catastrophic complication following the use of the Swan-Ganz catheter; it carries a mortality of 50% due to massive pulmonary hemorrhage.[9] This complication is more frequently observed in patients with pulmonary hypertension.

Intra-alveolar Hemorrhage

Intra-alveolar hemorrhage is observed in leptospiral and dengue infections, in pulmonary vasculitis, autoimmune diseases, Goodpasture's syndrome, Wegener's granulomatosis, bleeding disorders, acute infections and in other idiopathic systemic disorders. Whatever the etiology, the presenting features are hemoptysis, alveolar infiltrates on chest X-ray, dyspnea and hypoxemia. The degree of hemoptysis need not always be a guide to the severity of intra-alveolar hemorrhage.

Vascular Anomalies

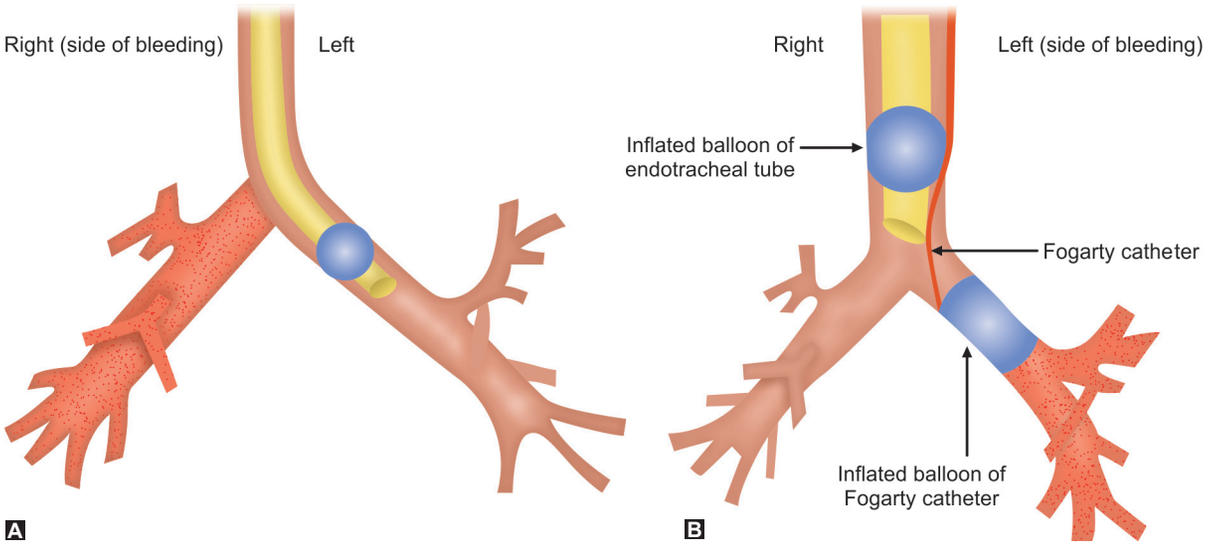
Arteriovenous malformations may rarely cause massive fatal hemoptysis.

Cryptogenic Hemoptysis

About 15% of patients with massive hemoptysis even after extensive investigation have no detectable cause of their hemoptysis, and are labeled as cryptogenic hemoptysis. Patients with massive cryptogenic bleeds generally stop bleeding spontaneously, and require only supportive care. A periodic follow-up is mandatory in these patients.

CLINICAL FEATURES

The clinical features of massive hemoptysis are related to: (1) aspiration of blood into the lungs which can cause hypoxemic respiratory failure due to interference with gas exchange; (2) effects of blood loss. Lethal hemoptysis more often than not kills because of aspiration of blood into the lungs, the patient literally drowning in his own blood, rather than dying because of blood loss.



Figs 1A and B: Unilateral lung ventilation using endotracheal balloon tamponade. (A) In bleeding from the right lung, an endotracheal tube advanced into the left main bronchus permits selective ventilation of the left lung and prevents spill-over of blood from the right into the left lung. (B) In bleeding from the left lung, a Fogarty balloon catheter is passed on the outside of the endotracheal tube to a point below its lower end. After guiding the Fogarty catheter into the left main bronchus, the balloon is inflated. The right lung is thus ventilated by the endotracheal tube, and bleeding from the left side is prevented from spilling into the right lung

Source: Modified from Winter SM, Ingbar DI. Massive hemoptysis: pathogenesis and management. J Intensive Care Med. 1988;3:171-88.

Clinical examination may occasionally reveal focal signs pointing to the site of the bleed. Auscultation of the heart, specifically for the tell-tale murmur of mitral valve disease should always be done.

DIAGNOSIS AND MANAGEMENT[10] (FIG. 1)

The immediate diagnostic step in a patient admitted to the ICU for massive hemoptysis is to determine whether the source of bleeding is from the upper gastrointestinal (GI) tract or from the respiratory tract. A thorough history, clinical examination and examination of the material coughed up, generally suffice. The blood in hemoptysis is bright red, frothy and alkaline. Once the intensity of hemoptysis lessens, the patient often continues to cough up sputum mixed with blood or coughs up blobs of bright red blood. In some instances, both bronchoscopy and an upper GI scopy are necessary to ascertain the source of the bleed. It is to be remembered that in severe hemoptysis, a patient may swallow large quantities of blood. Hematemesis (if he vomits) and melena may then follow. Similarly, a patient with severe hematemesis may aspirate blood into the lungs, and this may result in cough with expectoration of blood. Blood in the mouth can also come from the sinuses, the nasal passage and the upper airway, i.e. the pharynx and from above the vocal cords. Upper airway bleeding can be easily missed if not carefully sought.

The next step in diagnosis is to determine whether the bleeding is from the right or left lung—i.e. to lateralize the bleed and also if possible to determine the lobe or the segment of a lobe from which the blood arises. Diagnostic steps may also reveal the etiology of the bleed. A baseline history, physical examination and a chest X-ray are mandatory. Focal signs over a lobe or a lung may well lateralize the bleed; similarly a chest X-ray may point to the lung or even the lobe involved. However, in our experience, in a truly massive hemoptysis it is frequently impossible to localize the lung or the lobe from which bleeding has occurred either on clinical examination or on a chest X-ray. This is because aspiration of blood into both lungs can result in diffuse or false localizing signs, and similarly an X-ray of the chest may show shadows related to aspiration of blood, rather than to the pathology causing the bleed.

Routine use of computed tomography (CT) chest in massive hemoptysis is usually unrewarding. Aspirated blood often obscures the underlying lesion, or may result in a misleading mass-like effect. CT of the chest may detect arteriovenous aneurysms, cavitative lung disease not apparent on a plain X-ray of the chest, and bronchiectasis. Haponik et al.[11] noted that a CT of the chest did not obviate the need for bronchoscopy in any patient. They also noted that an X-ray chest and bronchoscopy provided all the information necessary for diagnosis and management in 94% of patients.[11]

Immediate priorities The immediate priorities in the management of a truly massive hemoptysis are to maintain and protect a clear airway and to stabilize the hemodynamic state. These priorities should be established even before initiating diagnostic steps to determine the cause and site of the bleed. It should be decided whether the patient needs to be intubated for protection of the airway, proper suctioning, for maintaining adequate oxygenation and gas exchange, and for protection against sudden cardiorespiratory arrest.

If intubation is decided upon, a large-sized (No. 8) endotracheal tube should be used. This facilitates easy suction and permits bronchoscopic evaluation through the large endotracheal tube.

Resuscitation A volume load with either colloids or crystalloids may be immediately necessary to restore blood volume, and arrangements to replace the lost hemoglobin with whole blood or packed cells should be made.

Once the airway has been established and hemodynamic stabilization is achieved, diagnostic and therapeutic procedures should be promptly carried out, even if the bleeding has lessened, as recurrence of brisk bleeding is both possible and unpredictable.

If the bleeding is not massive and life-threatening, a detailed history and physical examination can precede more considered diagnostic procedures, including bronchoscopy. Routine laboratory investigations include a chest X-ray, urine examination, blood count, packed cell volume (PCV), blood urea nitrogen, serum creatinine, platelet count, bleeding time, coagulation profile, blood grouping and cross-matching, arterial pH and arterial blood gas analysis. Sputum should be examined for acid-fast bacilli, other bacteria, and should be cultured. Sputum should also be sent for fungal stains and cultures in appropriate clinical conditions. Sputum cytology is important if there is suspicion of a carcinoma. Other special tests may need to be performed depending on the clinical situation. Tests for autoimmune diseases, and for the detection of antiglomerular basement membrane antibodies, are necessary in patients with hemoptysis and intra-alveolar hemorrhage. The presence of massive intra-alveolar hemorrhage should also prompt tests for leptospiral infection (CPK level in blood and serology).

Vital signs should be closely monitored in the ICU, and the patient should be sufficiently sedated with morphine, 5–7.5 mg subcutaneously or 2 mg intravenously, or with buprenorphine 0.2 mg intravenously, to allay anxiety, restlessness, and to prevent unnecessary coughing. However, the patient should not be oversedated, and the cough reflex should not be unduly depressed; this can lead to accumulation of blood within the lungs, with serious impairment of gas exchange.

Localization of the Site of Bleeding and Therapeutic Measures to Stop Bleeding

Bronchoscopy[12,13]

Early bronchoscopy is advocated preferably during active bleeding, with three specific objectives—(1) to determine from which lung the bleeding occurs, (2) to determine the site (i.e. the lobe or segment) of the bleed, and if possible, (3) to determine the cause or pathology. In patients with lateralized or localized bleeding detected on bronchoscopy, the following therapeutic bronchoscopic procedures may help to stop the bleeding—

- *Topical therapy* Topical thrombin and fibrinogen-thrombin solutions have been successfully used to stop bleeding in massive hemoptysis.[14] The bleeding may stop permanently or temporarily. This procedure allows time for further evaluation and future planned elective therapy if necessary. Topical epinephrine (1:20,000) has been used to treat hemoptysis secondary to transbronchial biopsy, but its efficacy in massive hemoptysis has not been proven. It would be perfectly justifiable to apply epinephrine over visibly bleeding lesions.
- *Bronchial irrigation* Conlan et al.[15,16] in a study in South Africa used endobronchial irrigation and lavage with iced saline to arrest bleeding in 23 patients with massive hemoptysis. 50 mL aliquots of iced saline arrested the bleeding in all patients, and the average volume of irrigation fluid required per patient was 500 mL.[16] The iced saline presumably acts by inducing localized vasoconstriction with stoppage of bleeding.

Balloon Tamponade

Endobronchial balloon tamponade has successfully arrested bleeding in massive hemoptysis for prolonged periods of time. A fiberoptic bronchoscope is used to guide a 4 Fr 100 cm long Fogarty balloon catheter, which is then inflated in a segmental or subsegmental bronchus leading to the site of bleeding. The balloon is kept inflated for 24–48 hours. If bleeding has stopped on deflating the balloon, and no further bleeding occurs after 6–8 hours of further observation, the balloon can be removed. Balloon tamponade is helpful in preserving gas exchange in the non-bleeding lung in patients with massive hemoptysis. This technique can also be used as a stop-gap measure to support the patient before arteriographic embolization or surgical resection. Balloon tamponade in the manner described above, can however produce ischemic mucosal injury and pneumonia in the obstructed segment.

Unilateral Lung Ventilation

If bronchoscopy can only lateralize the lung from which bleeding occurs without exactly localizing the bleeding segment or lobe, a modified balloon tamponade technique may be employed. The patient is first intubated with a large bore endotracheal tube. The bleeding site is lateralized by a flexible or rigid bronchoscope. If the right lung is bleeding, the endotracheal tube is advanced into the left main bronchus, permitting ventilation of the left lung only, and preventing aspiration of blood from the bleeding right lung into the left side (Fig. 1A). If the left lung is bleeding, a Fogarty balloon catheter is passed on the outside of the endotracheal tube, to a point below the lower end of the endotracheal tube. Through a fiberoptic bronchoscope passed via the endotracheal tube, the tip of the Fogarty balloon catheter is now guided into the left main bronchus, and the balloon is then inflated. The fiberoptic bronchoscope is now removed. The endotracheal tube now serves to ventilate the right lung, and blood from the bleeding left lung is prevented from being aspirated into the right lung (Fig. 1B). Selective intubation of the right lung carries the danger of occluding the right upper lobe bronchus orifice.

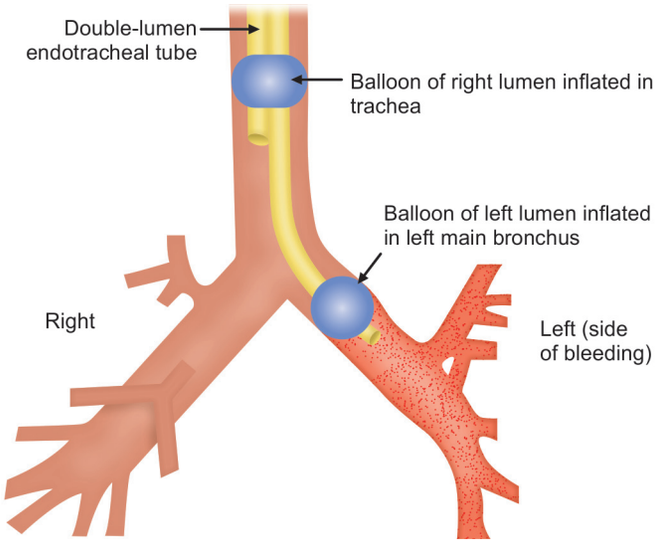

Double-lumen endotracheal tube
Balloon of right lumen inflated in trachea
Balloon of left lumen inflated in left main bronchus
Right
Left (side of bleeding)

Fig. 2: Schematic representation of proper placement of a left-sided double lumen endotracheal tube. The inflated ballon in the trachea allows ventilation of the right lung. The inflated balloon in the left main bronchus prevents spill-over from left into right side

Unilateral ventilation is often unsuccessful in maintaining satisfactory gas exchange, particularly if aspiration of blood has already occurred into the non-bleeding lung.

Double-Lumen Endotracheal Tubes

In very selected situations, separation of the two lungs can be achieved by double lumen endotracheal tubes (Fig. 2). These tubes are often extremely difficult to place, and need an experienced and skilled anesthetist. There is danger of the tube getting blocked by secretions and clotted blood. It is often impossible to pass a fiberoptic bronchoscope through the small lumen to verify the position of the tube. If successfully placed, both lungs can be ventilated independently, and aspiration of blood from one lung to the other is prevented. The patient often needs to be paralyzed to allow efficient ventilation. Other complications include dislodgment of the tube, and tracheobronchial rupture from use of too large a tube, or overinflation of the balloon.

Positioning of the patient A patient with massive hemoptysis should be positioned with the bleeding lung down so as to confine the blood to that lung and prevent aspiration into the other. Once an airway is established, patient position is controversial. Blood could clot in the dependent lung and in the airways of that lung causing a permanent atelectasis. If bleeding is from the pulmonary circulation, placing the bleeding lobe or lung higher would, through gravity, perhaps lessen bleeding by creating zone I conditions in which alveolar pressure is higher than the pulmonary artery pressure.

In very brisk bleeds, a bronchoscopic evaluation often fails to lateralize the side of the bleed. This happens when the briskness of bleeding outstrips or is faster than what can be removed by suction, so that vision through the bronchoscope is obscured. A rigid bronchoscope may then be of greater value, as more efficient suction is possible through it. Even so, bronchoscopy at times fails to be of diagnostic help, and is unable to lateralize and localize the site of bleed.

Arteriography and Embolotherapy[17-19]

We have no experience with either unilateral ventilation or double lumen endotracheal tubes in the management of massive hemoptysis. Therefore, if bronchoscopic examination allows identification of the site of the bleed, and if the bleed cannot be controlled by topical methods used via the bronchoscope, we go immediately for arteriography. Arteriography is also promptly done if bronchoscopy fails to lateralize the bleed and localize its site. Initially bronchial arteriography is done. It should be noted that non-bronchial systemic collateral vessels from the axillary, subclavian and internal mammary arteries can also feed into diseased areas of the lung, and be responsible for massive hemoptysis. Once the bleeding site is identified by arteriography, embolotherapy is performed at the same sitting. The bleeding should stop; if it persists the pulmonary arteries are examined angiographically, and if a bleeding site is determined, embolotherapy is performed to stop the bleed. Successful long-term control of bleeding after embolization ranges 70–88%, with follow-up periods ranging 1–60 months.

Successful embolization depends on the interventional radiologist's experience and expertise. Technical failure occurs in 4–13% of attempted embolizations because of failure to cannulate the artery. If the anterior spinal artery branch arises from a bleeding bronchial artery, embolization should be avoided as it could otherwise cause spinal cord injury and paralysis. When the position of the tip of the catheter is unstable, reflux of embolic material into the aorta has resulted in systemic embolization, with dangerous complications due to embolic infarction of other organ systems.

Recurrent hemoptysis generally indicates incomplete embolization due to incomplete evaluation of systemic collaterals seen frequently in patients with mycetoma and in tuberculous disease. Recurrent hemoptysis could also be due to bleeding from the pulmonary vessels.

Surgery

Surgery is indicated in the following situations—

- In uncontrolled massive hemoptysis when the site of bleeding has been lateralized, and preferably localized to a segment or lobe.
- When embolization is not available or feasible, or when the patient continues to bleed in spite of embolization. The site of bleeding needs to be established by diagnostic bronchoscopy.
- When bleeding from a known site within a lung is associated with persistent hemodynamic instability and respiratory compromise.

- As definitive therapy in patients whose hemoptysis has stopped or has markedly reduced, and who are hemodynamically stable.

We would prefer to avoid immediate definitive surgery in patients whose bleeding has ceased spontaneously, or following bronchoscopic procedures, except under exceptional circumstances. Elective surgery is perhaps best planned at a later date when the patient's condition has improved significantly.

Surgery is contraindicated under the following circumstances—

- In the presence of well-marked arterial hypoxemia and carbon dioxide retention.
- In patients with poor pulmonary reserve, with dyspnea at rest, or on slight exertion.
- In bilateral lung disease.
- Inability to lateralize and localize the site of bleeding.
- In patients with diffuse disease as in multiple arteriovenous aneurysms or malformations, cystic fibrosis and non-localized bronchiectasis.
- In patients with pulmonary hypertension—a mean pulmonary artery pressure greater than 30 mm Hg is a contraindication to surgical resection.

If surgery is decided upon, a few basic investigations need to be done to assess the risk and fitness for surgery. Bedside spirometry to measure the FVC and FEV_1, and in doubtful cases quantitative ventilation-perfusion scanning may be used to predict the cardiac output and the ventilation directed toward the portion of lung that is to be resected. The postoperative FEV_1 can be predicted from the above information. A predicted postoperative FEV_1 of less than 800 mL contraindicates surgery because of the high risk of persistent severe postoperative respiratory failure.

Postoperative complications are common and include the necessity for prolonged ventilatory support, bronchopleural fistula, infection and recurrent pulmonary hemorrhage. The overall mortality ranges from 10% to 50%. Active bleeding at the time of surgery is associated with a greater degree of morbidity and mortality, probably related to an increased risk of aspiration. As far as possible, surgery, if decided upon, should be done in between episodes of bleeding in massive hemoptysis, as this significantly reduces morbidity and mortality.

Better techniques in bronchial vessel embolization and in other non-surgical bronchoscopic therapeutic procedures have reduced the need for emergency surgery in the management of massive hemoptysis.

MANAGEMENT OF SEVERE IATROGENIC HEMOPTYSIS

Massive Hemoptysis Due to Tracheoarterial Fistula[10]

This is generally fatal, if the tracheostomy tube erodes the inominate artery. The following steps should be tried—

- Overinflate the cuff in the hope that tamponade is achieved over the bleeding site.
- Apply downward and forward pressure on top of the tracheostomy tube, tamponading the potential bleeding point at the stoma.
- If bleeding slows or stops, an endotracheal tube should be placed distal to the tip of the tracheostomy tube. Ideally a surgeon should be present when the tube is removed.
- If bleeding restarts the surgeon can attempt a finger tamponade of the inominate vessel against the sternum.
- A definitive repair in the theater should be undertaken by the surgeon as soon as possible.

Iatrogenic Rupture of the Pulmonary Artery during a Swan-Ganz Catheterization[20]

A balloon tamponade of the ruptured vessel with the Swan-Ganz catheter is helpful. The balloon is first deflated; the catheter is withdrawn 5 cm and the balloon inflated with 2 mL air. It is then allowed to float back into the bleeding vessel so as to occlude it. The patient should be immediately intubated in the main stem bronchus opposite to the involved lung, to minimize aspiration. More often than not death occurs from bleeding before this can be accomplished.

If bleeding is reduced or arrested an urgent angiography is performed to detect the site of tear. Embolization of the affected vessel is performed if a tear or pseudoaneurysm is present.

MANAGEMENT OF SEVERE INTRA-ALVEOLAR HEMORRHAGE

Selective arterial embolization is obviously not possible. For immunologically mediated disease, corticosteroids, cytotoxic agents, plasmapheresis are available options.

To start with methylprednisolone is given in a dose of 1 g intravenous (IV) daily for 3 days followed by oral prednisolone 1 mg/kg per day for a week, the dose being gradually tapered down to a maintenance dose of 10 mg/day. Corticosteroids are often combined with cytotoxic drug therapy in the management of vasculitides and immunological lung disorders.

Recombinant factor VIIa has been used successfully for treatment of diffuse alveolar hemorrhage due to disseminated aspergillosis, bone marrow transplantation, small vessel vasculitis and cystic fibrosis.[21,22]

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CHAPTER 36

Diseases of the Pleura in the Critically Ill

PNEUMOTHORAX IN THE INTENSIVE CARE UNIT

The most important cause of pneumothorax in the intensive care unit (ICU) is iatrogenic, related to invasive procedures or to barotraumas. Patients with secondary pneumothorax due to pre-existing lung disease may also be admitted or transferred to the ICU because of increasing respiratory distress and hypoxemia. Tension pneumothorax always necessitates intensive care; its early diagnosis and prompt treatment make the difference between life and death. Patients with trauma to the chest often receive critical care as besides suffering a pneumothorax they may have an injury to the chest wall, lung or mediastinal structures.

Iatrogenic Pneumothorax

Insertion of a Central Venous Catheter

The most common cause of iatrogenic pneumothorax in the ICU is following insertion of a central venous catheter in the subclavian or the internal jugular vein. The pleural complications following insertion of a central venous catheter have been discussed earlier in the Section Procedures and Monitoring in the Intensive Care Unit. Most pneumothoraces occur at the time of the procedure due to direct lung puncture, but delayed pneumothoraces are not uncommon. Therefore, a radiographic examination of the chest should be done not only soon after the procedure but also 12–24 hours later. If a small pneumothorax is diagnosed and the patient is asymptomatic and not on mechanical ventilator support, the catheter need not be removed, provided repeated radiography of the chest shows that the leak has not increased. If however the patient is being mechanically ventilated, or the pneumothorax is large, or the patient is symptomatic, or shows gas exchange abnormalities, the central line should be promptly removed and a tube thoracotomy performed as soon as possible.

Barotrauma

An important cause of pneumothorax in the ICU is barotrauma caused by mechanical ventilator support. Barotrauma occurs in 3–10% of patients on mechanical ventilation and includes interstitial emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum and subcutaneous (surgical) emphysema. The most frequent and most clinically important of all these is pneumothorax[1] which occurs in 1–15% of all patients on mechanical ventilation. The number of ventilator days, aggressive ventilator strategies, the degree of positive end-expiratory pressure (PEEP) used, and underlying disease [chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), necrotizing pneumonia] all influence the incidence of pneumothorax.[2] When pneumothorax occurs during mechanical ventilation more than 30% develop tension pneumothorax.[2]

The early sign of barotrauma during mechanical ventilation is interstitial emphysema, manifest as linear air streaks within the interstitium and by a perivascular air halo. Subpleural air cysts may also be present and warn of impending pneumothorax. The latter may however occur without any radiological evidence of interstitial emphysema or subpleural cysts. Ultrasonography has been shown to help in the bedside diagnosis of pneumothorax. The absence of lung sliding on an ultrasonographic examination of the chest is believed to denote a pneumothorax[3] although false-positive signs may occur in patients with emphysematous bullae or in patients with pleural adhesions.

Whenever radiographic evidence of barotrauma is detected, without the occurrence of a pneumothorax, ventilatory settings must be suitably modified (lowered PEEP, lower tidal volumes) and increased sedation considered. A close clinical and radiological follow-up is necessary in anticipation of a pneumothorax.

Tension Pneumothorax

Tension pneumothorax in the ICU is most frequently observed when pneumothorax results in patients on mechanical ventilation. It may however also occur in secondary pneumothorax or in a primary pneumothorax. It is characterized by air entering the pleural space during inspiration, but because of a check-valve mechanism at the site of rupture, little or no air can gain egress back into the lung and hence to the outside during expiration. The intrapleural pressure continues to increase and causes rapid cardiorespiratory collapse.

The patient is tachypneic, breathless, cold, clammy, extremely distressed and gasping for air. The markedly increased intrapleural pressure together with the marked mediastinal shift to the opposite side hinders venous return. Hence, there is marked tachycardia and hypotension. The total collapse of the lung, together with the preservation of a fair degree of blood flow through it leads to a large right to left shunt within the collapsed lung so that there is increasing hypoxia, cyanosis and increasing respiration failure. The markedly increased intrapleural pressure on the affected side is transmitted to an extent to the contralateral pleural space so that the lung function of the contralateral side is also adversely affected. Ultimately, if the tension pneumothorax is not promptly relieved, there is well-nigh stoppage of venous return because of a tamponade-like effect on the heart. A cardiac arrest often associated with an electromechanical dissociation on the electrocardiogram (ECG) is the end result.

Diagnosis[4]

Tension pneumothorax is a dire emergency and diagnosis should be clinical, at the bedside. Tachypnea, tachycardia, and respiratory distress with absent breath sounds on the affected side are observed. A hyper-resonant note on the affected side may be missed if the tension within the pleural space is marked. The heart and mediastinum are shifted to the opposite side.

Tension pneumothorax in a patient on mechanical ventilator is characterized by the sudden appearance of respiratory distress, apprehension, tachycardia, tachypnea, hypotension, cyanosis or a sharp fall in O_2 saturation. The patient clashes continuously with the ventilator, is restless, cold, clammy and there is a marked increase in both peak pressure and pause pressure, decreasing compliance and increasing auto PEEP. Difficulty in bagging the patient with an Ambu bag or providing adequate tidal volumes is also noted. Breath sounds are absent on the ipsilateral side. It should be noted that at times breath sounds heard on the normal side may be transmitted to the affected side, particularly in patients on ventilator support (see Chapter Procedures in the Intensive Care Unit).

The diagnosis in comatose patients or in patients who already are critically ill (before the event) may be delayed. Sudden unexplained hypoxia and tachypnea in these patients should always arouse suspicion of a possible tension pneumothorax.

Treatment[4]

Treatment should not be delayed and should not await radiographic confirmation if the clinical features described above are present. This is particularly crucial in patients receiving mechanical ventilation, as death due to quickly mounting intrapleural tension can otherwise result in minutes. If a chest tube is not immediately available, a large bore needle is pushed into the pleural space through the second intercostal space in the midclavicular line. A rush of air is noted on entering the pleural space. A large intercostal drainage chest tube can then be placed and connected to a drainage system to drain the large air leak that is invariably present if the patient is on mechanical ventilator support (see Chapter Procedures in the Intensive Care Unit).

Once intrapleural tension falls, there is a rapid relief in symptoms and signs. The tachycardia subsides, the blood pressure rises and oxygen saturation and PaO_2 increase very significantly. If the patient is on the machine, the peak and plateau pressures fall and the compliance improves. Ventilator settings may need modification to allow good gas exchange and at the same time minimize the air leak into the pleura. The sooner the ventilator is removed the quicker the healing of the tear in the pleura.

Secondary Pneumothorax

Secondary pneumothorax must be drained through intercostal tube drainage even if the pneumothorax is small. Aspiration should be considered only in asymptomatic small pneumothoraces. Air leak may often persist in a secondary pneumothorax so that the lung may take more than 7 days to expand even with adequate drainage. Surgical intervention may be necessary if the lung fails to expand; chemical pleurodesis is an alternative approach.

Bronchopleural Fistula[5]

A bronchopleural fistula is characterized by a communication between the bronchial tree and the intrapleural space. A bronchopleural fistula is diagnosed when there is a failure of the lung to expand in spite of adequate chest tube drainage of the pneumothorax. This is observed in some patients who suffer a pneumothorax during ventilator support, in a few patients following trauma to the chest, or following diagnostic and therapeutic procedures such as thoracic surgery.

In a critical care unit, the most common cause of a bronchopleural fistula is barotrauma during mechanical

Box 1: Management of pneumothorax with a bronchopleural fistula

- Drain pneumothorax with a large-bore drain: avoid suction or use very soft suction—else air leak will increase
- Reduce "steal flow" (which is the difference between inspired volume and expired volume) by keeping the diseased lung in dependent position
- Monitor "steal flow"
- If on ventilator support—
  - Reduce tidal volume, go off positive end expiratory pressure
  - Reduce inspiratory time and if possible the tidal volume
  - If possible, allow spontaneous respiration, using bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP)
- If air leak is not reduced over time, attempt to seal site of leak with a fibrin seal through a bronchoscope
- If the above measures fail—
  - Surgery, if patient's condition allows
  - Double lumen intubation for single lung or differential ventilation

ventilation causing a large communication between a fair-sized bronchus and the pleural space. This occurs particularly in the presence of serious underlying parenchymal lung disease—for example, ARDS or necrotizing pneumonia.

For all practical purposes, if in a patient with pneumothorax, there is a continuous air leak for more than 24–48 hours in spite of adequate chest tube drainage, a bronchopleural fistula exists. If a patient is on ventilator support, a persistent large air leak results in failure of lung re-expansion, loss of delivered tidal volume, inability to use PEEP and alveolar hypoventilation which results in hypercapnia.

Management[5]

The management of a bronchopleural fistula is summarized in Box 1.

PLEURAL EFFUSIONS IN THE CRITICAL CARE UNIT

It is not the purpose of this section to elaborate on the subject of pleural effusion. Relevant points in relation to pleural effusion in the critical care unit need to be kept in mind.

- There needs to be a collection of near 350–500 mL of pleural fluid before it can be clinically detected. The most constantly present physical finding over pleural fluid is diminished or absent breath sounds. A stony dull note is present if there is at least 500 mL of pleural fluid.
- In the ICU, the best way to detect a suspected pleural effusion is through ultrasonography of the chest.
- Pleural effusions are caused not just by diseases within the lungs; they can be due to systemic causes and to diseases of the heart, liver and kidneys.
- The only way to distinguish between a pleural transudate and exudate is by doing a diagnostic tap and examining the pleural fluid. Light's criteria enable one to make this differentiation.
- Pleural exudates as defined by Light's criteria have one or more of the following criteria—
  - The total protein in the pleural fluid divided by the total serum protein is more than 0.5.
  - The lactate dehydrogenase (LDH) of the pleural fluid divided by the LDH in the serum is more than 0.6.
  - The LDH of the pleural fluid is greater than two-thirds of the upper limits of the normal LDH in the blood.
- Pleural transudates have none of the above features. In addition, pleural exudates have high cell counts.
- One must be wary of the fact that a pleural transudate—say due to heart failure, may occasionally show a higher protein content than expected if the patient has been diuresed significantly by a diuretic, like furosemide.
- The intensivist needs to know the common causes of pleural effusion encountered in the ICU.
- In most medical ICUs, transudates are more common than exudates. The important causes of transudates are—
  - Congestive cardiac failure; this is the most common cause of bilateral pleural transudates.
  - Hypoalbuminemia from any cause can also result in bilateral transudates. Renal disease and cirrhosis of the liver are two other important causes of pleural transudate.
  - Atelectasis may also be associated with a small pleural effusion which on examination is a transudate.
  - Ascitis due to hepatic dysfunction can track into mainly the right chest through pores present on the right dome of the diaphragm leading to a pleural transudate. At times, the presentation is with more fluid in the chest and much less in the abdomen.
- There are many causes of pleural exudates encountered in medical and surgical ICUs. The presence of an exudate should prompt a careful physical examination not just confined to the lungs but to all other organ systems. Special relevant investigations may be necessary to make a complete diagnosis.
  - The most important and frequent cause of a pleural exudate is pneumonia—either community acquired, nosocomial, or aspiration.
  - Other important causes are pulmonary embolism (the pleural fluid is often hemorrhagic), pancreatitis, postmyocardial infarction, esophageal rupture, pleural effusion secondary to a subdiaphragmatic pathology—as for example, a liver abscess or a subphrenic abscess. Mitotic lesions involving the lung or pleura may present with a pleural effusion which on examination is an exudate.

The important causes of exudates and transudates constituting a pleural effusion are listed in Box 2 and Box 3, respectively.

At times, the pleural fluid is blood stained as in pulmonary infarction, malignancy involving the lungs, pleura, and rarely in tuberculosis.

Box 2: Causes of pleural exudates

- Infections—
  - Tuberculosis
  - Other infections
  - Bacterial
  - Viral
  - Nocardial
  - Fungal
  - Parasitic
- Malignancies—
  - Pleural metastasis
  - Lymphoma
  - Pleural mesothelioma
- Vascular—
  - Pulmonary embolism
  - Vasculitides
- Gastrointestinal (GI) diseases—
  - Pancreatitis
  - Pancreatic pseudocyst
  - Perforation of the esophagus
  - Intrahepatic or subphrenic abscess
- Inflammatory (noninfectious)—
  - Asbestosis
  - Radiation
  - Uremic
  - Post-thoracotomy
  - Post-transplant
- Connective tissue diseases
- Iatrogenic, traumatic (including hemothorax)
- Miscellaneous—
  - Lymphangioleiomyomatosis
  - Meig's syndrome
  - Yellow nail syndrome
  - Chylothorax

Box 3: Causes of pleural transudate

- *Common causes*—
  - Congestive heart failure
  - Cirrhosis of liver
  - Nephrotic syndrome
  - Hypoalbuminemia from any cause
  - Continuous peritoneal dialysis
- *Uncommon causes*—
  - Superior vena caval obstruction
  - Constrictive pericarditis
  - Hypothyroidism
  - Atelectasis
  - Urinothorax
  - Budd-Chiari syndrome

A hemothorax generally results following blunt and penetrating chest trauma, invasive procedures, malignancy, hemorrhagic disorders and the use of anticoagulation.

The presence of chyle (rarely seen in the ICU) is suggested by the presence of milky pleural fluid, the presence of chylomicrons and triglycerides more than 110 mg/dL.

A diagnostic pleural tap if performed under ultrasound guidance with meticulous attention to technique should not cause complications. Pneumothorax has however been reported in 4–30% of cases.[6] Liver or splenic puncture may occur if the patient is not sitting upright but is recumbent during the procedure. Recumbency leads to the migration of the abdominal viscera upward. The upward displacement of abdominal viscera is however easily detected by ultrasonography, so that this complication of accidental splenic or liver puncture should be prevented if the diagnostic tap is done under ultrasonic guidance. A relative contraindication for a diagnostic tap is the presence of a bleeding disorder.

A diagnostic pleural tap of a small pleural effusion when the patient is on mechanical ventilator support risks a pneumothorax. The tap should always be done under ultrasound guidance and the ventilator turned off very briefly just before the needle enters the pleural space. It can be restarted the moment the needle is withdrawn.

THERAPEUTIC THORACOCENTESIS

The primary indication for a therapeutic thoracocentesis is the relief of dyspnea. The major relative contraindication of thoracocentesis is a bleeding diathesis or anticoagulation. The danger of a pneumothorax is significant if therapeutic thoracocentesis is attempted in patients on mechanical ventilator support.

It is best not to remove more than a liter and a half at one time. The occurrence during the procedure of cough, breathlessness, tightness in the chest is an indication to stop the paracentesis. A precipitous drop in pleural pressure to less than –20 cm H_2O can cause problems. This is almost always avoided if the fluid removed is not in excess of a liter or so at one time.

Complications of therapeutic paracentesis are pneumothorax, bleeding, particularly if the patient has a bleeding tendency and the introduction of secondary infection, if an aseptic technique is not followed.

There are three complications which are unique to thoracic paracentesis. They are hypoxemia, unilateral pulmonary edema and hypovolemia. Hypoxemia occurs because of worsening ventilation perfusion ratios despite relief of dyspnea. It is related to occult or clinical pulmonary edema in the ipsilateral lung. Ipsilateral acute pulmonary edema occurs as a complication when the collapsed lung (particularly if it has remained collapsed for weeks or months) quickly expands following rapid removal of pleural fluid. The increased negative pressure within the pleural space causes transudation of fluid into the alveoli resulting in pulmonary edema. This negative pressure pulmonary edema causes breathlessness, which may manifest during the withdrawal of fluid, or minutes or even hours after withdrawal. A slower removal of fluid restricted generally to about a liter at a time generally prevents these complications.

The reason for the relief of dyspnea following thoracic paracentesis is debatable. It cannot be explained solely by an increase in PaO_2 as this increase is modest. In fact in some patients there is an initial fall in PaO_2 which subsequently rises. It also cannot be easily explained by an increase in the lung volume, as immediate changes in lung volume are modest and variable. Perhaps relief of dyspnea following thoracocentesis may be the result of decreased stimulation of lung, or chest wall receptors, or of both.[7-9]

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CHAPTER 37

Negative Pressure Pulmonary Edema

INTRODUCTION

Negative pressure pulmonary edema (NPPE), also called post-obstructive pulmonary edema (POPE), is a dangerous and potentially fatal condition, which is of particular relevance both in anesthesiology and critical care. It typically occurs perioperatively[1,2] following removal of the endotracheal tube. Very occasionally the patient has severe laryngeal spasm with resulting acute severe obstruction to the airway. The markedly increased negative intrapleural pressure and intra-alveolar pressure caused during breathing attempts against a closed glottis leads to transudation of fluid into the interstitium and alveoli of the lung with sometimes florid pulmonary edema.[3,4]

The NPPE that results from acute upper airways obstruction is termed NPPE type I. The incidence of NPPE I has been reported to be 0.05–0.1% of all anesthetic practices, though it is suggested that it perhaps occurs more frequently than is generally documented. NPPE I develops immediately or soon after the onset of acute upper airways obstruction.

Other causes of acute upper airways obstruction causing low pressure pulmonary edema include surgical manipulation of the upper airway,[5] strangulation, hanging, foreign bodies, upper airway tumors, croup, epiglottitis, migration of a Foley's catheter balloon into the larynx when the Foley's catheter is used to tamponade the nose in epistaxis. NPPE can also occur in near drowning accidents (due to intense laryngospasm), and following a blocked endotracheal or tracheostomy tube.[6]

Type II NPPE is believed to result following relief of upper airways obstruction caused by big tonsils, hypertrophic adenoids or a redundant uvula.

In adults, the most frequent and important cause of NPPE is postoperative laryngospasm.

PATHOPHYSIOLOGY[3,4,7,8]

The highly negative intrapleural pressure (as much as –40 to –100 cm H_2O compared to –3 to 10 cm H_2O) causes a dramatic increase in systemic venous return to the heart, associated with a fall in cardiac output due to reduced pulmonary venous drainage into the left atrium. The conjunction of increased capillary pressure with a markedly negative intra-alveolar pressure leads to fluid moving out from the vascular system first into the interstitial tissue spaces and then into the alveoli, resulting in pulmonary edema. Pulmonary edema persists even after the airway obstruction is relieved.

Pathophysiology of NPPE II

The pathophysiology of NPPE II is not quite clear. It is proposed that chronic upper airways obstruction leads to a modest level of positive end-expiratory pressure (PEEP) and increased lung volumes. Relief of obstruction removes PEEP, returning both lung volumes and pressures at end-expiration to normal. It is postulated that altered permeability and some degree of occult interstitial edema do not resolve immediately and that the removal of PEEP leads to interstitial fluid transudation and pulmonary edema. The explanation given above is rather feeble and unsatisfactory. NPPE II is not considered further in this section.

CLINICAL FEATURES OF NPPE I[9]

The symptoms of NPPE usually develop immediately after extubation though at times the onset may be delayed for

a few hours or even later.[10] The importance of close peri-operative and post-operative vigilance and care cannot be over-emphasized.

The onset of pulmonary edema is characterized by tachypnea, tachycardia, restlessness and respiratory distress. The oxygen saturation shows a sharp drop. Manifestations of acute upper airways obstruction include stridor, use of accessory muscles of respiration, retraction of suprasternal, supraclavicular areas and of the intercostal spaces during inspiration. Auscultation reveals crackles and wheezes. In severe cases pink frothy sputum literally wells out of the mouth. Arterial blood gases show a low PaO_2 (<60 mm Hg on room air); hypercapnia may be present. pH is often less than 7.3 both because of hypercapnia and at times due to lactic acid acidosis.

X-ray of the chest show frank pulmonary edema. There is comparatively little data with regard to the distribution of post-extubation pulmonary edema. High resolution computed tomography (HRCT) studies suggest there is a striking preferential central and non-dependent distribution of ground glass attenuation (edema) which parallels the pleural and interstitial pressure gradients.[11]

DIFFERENTIAL DIAGNOSIS

The diagnosis is promptly suggested by the history and the presence of laryngeal spasm. Symptoms usually occur immediately or within 1 hour of extubation, but occasionally may be further delayed. The major differential diagnosis particularly in elderly patients is acute left ventricular failure. It is possible that the stress of acute upper airways obstruction could decompensate a heart with underlying valvular, hypertensive or coronary artery disease. Acute respiratory distress syndrome (ARDS) does not enter into the differential diagnosis unless there is evidence of sepsis or prolonged surgery associated with multiple blood transfusions. Fluid overload during surgery should always be a consideration but none of these entities is associated with the features of an upper airway obstruction.

MANAGEMENT

Management consists of—

- Relief of hypoxia with oxygen through a high flow mask.
- Control of the airway is imperative if it continues to be obstructed. This would involve reinsertion of the endotracheal tube or performing a tracheostomy in the presence of a severe unrelenting laryngospasm. Attempts at reintubation by inexperienced anesthesiologists or intensivists can do more harm.
- Hypoxia and pulmonary edema causing acute respiratory failure (ARF) need ventilator support. In the milder cases noninvasive ventilator support using continuous positive airway pressure (CPAP) or biphasic positive airway pressure (BIPAP) may suffice. In the more severe cases invasive ventilator support is mandatory either after reintubation or following a tracheostomy. PEEP should be used; the value titrated to improve oxygenation without causing cardiovascular compromise. The fraction of inspired oxygen (FiO_2) should be increased (if necessary even to 100%) to ensure adequate relief of hypoxia.
- Intravenous frusemide is given in titrated doses or as a continuous IV infusion so that a urine output of 100 mL/hour (in adults) is maintained.
- Hypotension may need appropriate treatment with vasopressors and inotropes.

Very rarely NPPE may evolve into ARDS and multiple organ failure.[12]

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SECTION

9

Mechanical Ventilation in the Critically Ill

- Mechanical Ventilation in the Critically Ill
- Weaning from Ventilator Support

CHAPTER 38

Mechanical Ventilation in the Critically Ill

INTRODUCTION

Mechanical ventilation as a therapeutic intervention was first widely used during the poliomyelitis epidemic in Europe and the United States in the 1940s and 1950s. Since then there have been great advances in technology, so that negative-pressure ventilators that were used originally in the 1940s and 1950s have been replaced by increasingly sophisticated positive pressure machines.

The purpose of mechanical ventilation is to provide ventilatory support partially or fully by an external device to patients who cannot maintain an adequate gas exchange, as for example in acute respiratory failure. Ventilator support also reduces the oxygen cost of breathing. Mechanical ventilator support, however, has its own hazards; these include ventilator-induced lung injury, barotrauma, adverse hemodynamic changes and the potential for serious nosocomial infection.

Ventilator support to any critically ill individual requires expertise and round-the-clock supervision and care. Life in many such patients is totally dependent on the efficient working of a machine. A mechanical failure, accidental disconnection of the machine from the patient, or a sudden obstruction of the airway, are all potential disasters which can lead to sudden death or brain damage from protracted hypoxia. A patient on mechanical ventilator support must therefore never be left unattended even for a minute. Thus, the optimal and safe use of mechanical ventilation is only possible in intensive care units (ICUs). Though the standard of critical care (which includes ventilator support) has improved and continues to improve significantly at least in the large metropolitan cities of India, care provided in large public and district hospitals in India and many other developing countries leaves much to be desired. In fact, critical care units in the poor countries of the world are often mere apologies of what they ought to be, or are nonexistent. In the absence of a full-fledged ICU, the next best option is to use ventilator support in a patient who needs it, in a special or even a general ward, provided that the medical registrar and nurses are well-trained in ventilator management. We managed several decades back, to do this at one of the large public teaching hospitals in Mumbai, and salvaged a number of very ill patients who would otherwise have died. The need for all medical registrars (at least in the large hospitals of India and other developing countries) to be familiar with the use of mechanical ventilators is thus imperative. It is the duty of the medical and administrative staff of such hospitals to provide basic facilities, and train a team of doctors and nurses who can manage critically ill patients on ventilator support, even in the absence of well-equipped ICUs.

This chapter to start with briefly tabulates the physiological effects of mechanical ventilation. It then proceeds to discuss the indications and criteria for ventilator support, types of ventilators for intermittent positive-pressure ventilation (IPPV), and the management of ventilatory support. This is followed by a description of the different modes of ventilator support, and the use of positive end-expiratory pressure (PEEP) as an adjunct. Then comes a section on the complications of mechanical ventilation. The chapter ends with a discussion on noninvasive ventilator support and of respiratory monitoring during mechanical ventilation.

9

INDICATIONS FOR MECHANICAL VENTILATION (BOX 1)

In many ICUs, particularly in the smaller cities of India, there is yet a certain hesitation and trepidation observed regarding the use of mechanical ventilation in patients who need ventilator support. In other words, mechanical ventilation is started much later than it should have been in the natural history of a disease requiring ventilatory support. The other equally common misconception and error is to be in a tearing hurry to remove ventilator support in a critically ill patient. Such a premature withdrawal of ventilator support is love's labor's lost—the patient regresses from near recovery to a critical state, which again necessitates the use of the ventilator. Indications for mechanical ventilation are discussed below.

Established Acute Respiratory Failure

Early ventilator support is now initiated by all good units in patients with acute respiratory failure.[1] The criteria and timing for initiating support depend on the etiological agent producing acute respiratory failure, and above all, on the rate at which respiratory function is observed to deteriorate. Different diseases producing acute respiratory failure present their own special problems with regard to initiating mechanical ventilation, technicalities in maintaining ventilation, and difficulties in weaning the patient from ventilator support. It is therefore best from the practical point of view to consider the indications in acute respiratory failure, with reference to the different groups of diseases frequently encountered in the ICU.

Box 1: Indications for mechanical ventilation

A. Established acute respiratory failure—
   - Primary ventilatory failure where lungs are normal to start with, e.g. poisonings that depress the CNS, CNS and neuromuscular disorders (poliomyelitis, infective polyneuritis, myasthenia), snake bite, severe tetanus
   - Hypoventilating comatose patients
   - Acute pulmonary disease, e.g. fulminant pneumonia, acute lung injury (ARDS)
   - Fulminant pulmonary edema
   - Major or massive pulmonary embolism
   - Major or massive atelectasis
   - Patients with COPD in acute crisis, unresponsive to conventional therapy
   - Patients with acute severe asthma unresponsive to conventional therapy
   - Patients with severe respiratory muscle fatigue

B. Incipient respiratory failure—
   - Patients with excessive ventilatory demands
   - Obese patients who have undergone upper abdominal surgery, or poor risk surgical patients
   - Patients with acute/fulminant parenchymal lung disease with rapidly progressive impairment of pulmonary function and reserve
   - Respiratory muscle fatigue in critical illnesses

C. Low-output states—shock of any etiology

D. Purposeful hyperventilation—
   - To decrease intracranial tension in patients with head injury associated with increased intracranial tension
   - To reduce cerebral edema after CPR or massive CVA

Abbreviations: CNS, central nervous system; CPR, cardiopulmonary resuscitation; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease.

Ventilator Support in Primary Ventilatory Failure

The most common indication for mechanical ventilation is acute primary failure of ventilation. Ventilatory failure occurs commonly in poisonings that depress the central nervous system (CNS), in acute inflammatory and other diseases involving the CNS, in some patients with head injury, increased intracranial tension, poliomyelitis, acute infective polyneuritis and myasthenia gravis. Severe tetanus is an important cause of ventilatory failure in India. Neuromuscular paralysis following a krait or cobra bite is particularly common in South India. The lungs are normal to start with, but changes within the lungs (chiefly increasing widespread atelectasis), almost always occur if treatment is delayed. In many patients with neuromuscular disease, deterioration can occur suddenly, almost precipitously, with disastrous consequences. It is therefore wise to start early ventilatory support in these patients.

Ventilator Support in a Hypoventilating Comatose Patient

Deep coma is an indication for securing the airways with an endotracheal tube or a tracheostomy. Hypoventilation in such patients may be due to depressed respiratory drive or secretions causing obstructed airways or patchy atelectasis. Hypoxia and hypercapnia resulting from hypoventilation may further impair the conscious state, which in turn may further depress ventilation. Unless the patient is clearly hyperventilating, a deeply comatose patient is safer on mechanical ventilation.

Ventilator Support in Acute Pulmonary Disease

These patients are hypoxic due to hypoxemic acute respiratory failure. Typical examples are in acute lung injury (ALI), acute respiratory disorder syndrome (ARDS),[2] and fulminant pneumonia. Patients with acute pulmonary disease are difficult to ventilate. They have a strong respiratory drive, are often severely hypoxic, and fight the ventilator. An inability to maintain a PaO_2 of above 55 mm Hg while on oxygen at a flow rate of 6–8 L/minute, is an indication for initiating ventilator support. Other criteria for starting mechanical ventilation in these patients are dealt with later.

Ventilator Support in Fulminant Pulmonary Edema

Acute pulmonary edema, if fulminant, literally chokes the patient at the level of the alveoli. Mechanical ventilation is life-saving not only because it allows the maintenance of an adequate PaO_2, but perhaps also because the high inflation

pressures used to ventilate the lungs reduces the transudation of fluid from the alveolar capillaries into the alveoli. Ventilator support buys time during which diuretics like furosemide have a chance to act, and other corrective measures to treat the underlying cause of acute pulmonary edema may be profitably undertaken.

Ventilator Support in Acute Thromboembolic Lung Disease

Ventilator support is indicated if the PaO_2 is below 60 mm Hg on supplemental oxygen, particularly in the presence of shock.

Ventilator Support in Acute on Chronic Respiratory Failure in Patients with Chronic Airways Obstruction[3]

Many patients in this group are used to a low PaO_2 below 65 mm Hg, and a high $PaCO_2$ above 50–60 mm Hg. Ventilator support should not be used unless all other modalities of treatment have been of no avail, clinical deterioration is evident, and there is a further deterioration in the arterial blood gases and arterial pH. In such patients ventilatory support is fraught with difficulty, and requires experience and expertise.

Ventilator Support in Acute Severe Asthma[4]

Acute severe asthma is probably one of the most difficult problems for effective mechanical ventilation. Yet, ventilator support is life-saving in those cases of acute severe asthma not responding to corticosteroids, nebulized bronchodilators and other medical therapy.

Ventilator Support in Patients with Severe Muscle Fatigue

Severe muscle fatigue (involving the muscles of respiration), is an increasingly recognized and important cause of hypoventilation and respiratory failure. Muscle fatigue can occur in patients with primary neuromuscular disease involving the respiratory muscles. It occurs much more frequently in lung disease and in any condition (not necessarily involving the lungs), where ventilatory demands are excessive. The timing of initiating ventilator support in these patients is a matter of fine judgment. Altered blood gases or feeble ventilatory efforts are of course an immediate indication. Irregular breathing patterns, or the presence of a respiratory paradox in which the abdominal muscles move inward rather than outward during inspiration, point to excessive muscle fatigue. Respiratory alternans is characterized by alternate excursions involving the diaphragm and the intercostals, and is also a pointer to muscle fatigue. Another important pointer to impending disaster is the presence of apneic spells which are often forerunners of prolonged respiratory arrest. It is better to ventilate such patients even if the arterial blood gases are not significantly distorted, rather than wait for disaster to occur.

Factors, which precipitate and contribute to respiratory muscle fatigue are hypoperfusion of the muscles, hypermetabolic states leading to an increased work load on the muscles of respiration, hypoxia, electrolyte and acid-base disturbances, poor nutrition as in alcoholics, or those with chronic liver or renal disease, and in old, feeble, debilitated patients.

Incipient Respiratory Failure

Mechanical ventilation is increasingly being used in patients in whom some degree of respiratory failure is anticipated. Perhaps the most important group comprises patients who have to meet increased ventilatory demands, and who therefore sooner or later show evidence of respiratory muscle fatigue. This is typically seen in acute severe asthma, but can occur in numerous medical and surgical problems. It is difficult for a seriously ill patient to sustain a ventilatory rate of greater than 35–40/minute or a minute ventilation (V_E) greater than 10–12 L/minute for any prolonged period of time without increasing muscle fatigue and the danger of impending sudden respiratory failure.

There is a special category of surgical patients who frequently require ventilator support for impending or insidious respiratory failure. These are obese individuals who have undergone upper abdominal surgery. This often leads to fixed or splinted domes of the diaphragm resulting in a loss of volume in both lower lobes. These patients are markedly tachypneic, particularly in the presence of fever and infection; their V_E is often as high as 12–15 L/minute, and their respiratory rates between 35/minute and 45/minute. They maintain their arterial blood gases within the normal range for some length of time, but not uncommonly these patients go into sudden respiratory failure, deteriorate sharply, and pose problems in emergency intubation and ventilation. A quick anticipation of worsening problems calls for early intubation and ventilator support before such a disaster occurs.

Other susceptible patients in whom hypoventilation is a likely sequel include poor-risk surgical patients whose recovery from surgery or trauma is hindered by obesity, chronic lung disease, old age, debility and electrolyte imbalance. In all these patients, postoperative ventilatory support is merely an extension of surgical care in the operation theater. They may require mechanical ventilation for a period varying from a few hours to a few days, and are weaned off ventilator support when they can maintain adequate gas exchange on spontaneous breathing.

Similarly, in acute or fulminant parenchymal lung disease where the tempo of impairment of respiratory reserve and respiratory function is very rapid, it is best to anticipate events in advance to allow for elective intubation and ventilatory support.

Low-Output States and Septic Shock

Ventilator support is now always indicated in low cardiac output states as in cardiogenic shock, or for that matter in shock from any etiology. It is often used in septic shock, at times quite early in the natural history, when the march of events signifies a rapidly evolving dangerous clinical state. In shock from any

cause, and in low-output states of any etiology (for example, in advanced liver cell failure or multiorgan failure), tissue perfusion is inadequate in relation to tissue oxygen needs. Also, a low cardiac output is generally associated with a low PvO_2, which in turn is responsible for a low PaO_2. Shock of any etiology, which results in a low pulmonary artery pressure and diminished perfusion of the lungs leads to an increase both in the dead space (V_D)/tidal volume (V_T) ratio, as well as to a ventilation/perfusion imbalance. Ventilator support helps in two ways—

1. With an increase in FiO_2 (if needs be to 70–80%), the PaO_2 increases, and therefore both the arterial oxygenation and the arterial oxygen content rise.
2. The muscles of respiration are rested once the ventilator takes over the function of ventilation.

This prevents incipient respiratory failure from progressing to frank ventilatory failure, and even ventilatory arrest. In patients who breathe excessively, the oxygen cost of breathing is considerably increased. At rest, the normal work of breathing accounts for 2–3% of total oxygen consumption. This can increase in acute respiratory failure to as high as 35–40%. In low-output states, resting the overworked respiratory muscles through mechanical ventilation sharply reduces the oxygen cost of breathing and allows more oxygen to be diverted to vital organs starved of their oxygen supply. However, in critically ill patients, it is equally important to control fever, shivering, constant movement and restlessness, as these can all contribute to increased oxygen consumption, and thereby reduce the already meager available oxygen supply to the vital organs.

Mechanical Ventilation for the Specific Purpose of Hyperventilation

A comparatively rare indication for mechanical ventilation is to hyperventilate patients with head injury, when associated with increased intracranial pressure. Hyperventilating these patients reduces the $PaCO_2$, which leads to reduction in the cerebral blood flow, and hence in the intracranial pressure. Hyperventilation is generally combined with sedation and muscle paralysis to prevent coughing and clashing with the ventilator, as these could lead to a rise in intracranial pressure. Clinicians often prefer to manage unconscious neurological and neurosurgical patients with increased intracranial pressure, with controlled mechanical hyperventilation. The same approach is sometimes used to counter cerebral edema following resuscitation after a cardiopulmonary arrest or in patients with cerebral edema consequent to a massive cerebrovascular accident. However, the efficacy of hyperventilation in all the above-mentioned situations is temporary (generally not exceeding 48 hours) and debatable.

OBJECTIVE CRITERIA FOR INITIATING VENTILATOR SUPPORT IN ADULTS

The criteria enumerated in Box 2 are mere guidelines, and not sacrosanct rules. It is crucial to take the clinical picture, the evolution of the disease in a given patient, and the trend and rate of change in the parameters outlined below, into consideration. The parameters given in Box 2 apply to patients in ventilatory failure, and to respiratory failure occurring with acute lung disease; they are not applicable to patients with chronic obstructive airways disease. These patients even under normal or basal conditions may have a PaO_2 of 60 mm Hg, and a $PaCO_2$ between 55 mm Hg and 60 mm Hg. They are used to hypoxia and hypercapnia, and tolerate both rather well.

Box 2: Criteria for initiating ventilator support in adults

- Respiratory rate >35/min
- VC <10–15 mL/kg
- MV >10–12 L/min over a prolonged period
- Maximum inspiratory force <20 cm H_2O
- PaO_2 <60 mm Hg on nasal oxygen at 6–8 L/min and/or $PaCO_2$ >55 mm Hg
- Alveolar-arterial oxygen gradient >300–350 mm Hg on FiO_2 of 1
- V_D/V_T >0.6
- Visible excessive work of breathing in critically ill or debilitated patients
- Clinical evidence of respiratory muscle fatigue—
  - Poor chest excursions
  - Tachypnea
  - Respiratory muscle paradox, respiratory alternans
  - Apneic spells

Abbreviations: VC, vital capacity; MV, minute ventilation; V_D, dead space; V_T, tidal volume.

Types of Ventilators for Intermittent Positive Pressure Ventilation[5]

Ventilators in ICUs are either volume-cycled or pressure-cycled or time-cycled.

A volume-cycled, i.e. a volume-targeted ventilator, delivers a preset volume and continues to do so regardless of a change in the patient's airway resistance or lung compliance.

A pressure-cycled, i.e. a pressure-targeted ventilator, cycles to expiration after a specified preset pressure has been attained. Thus, gas flows into the lungs until a preset pressure limit is reached. The volume delivered will therefore change if the airway resistance and/or the lung compliance change.

In a time-cycled ventilator, the inspiratory phase ends when a predetermined time has elapsed. This time remains fixed, and is controlled by a timing mechanism within the ventilator, which is unaffected by conditions in the patient's lungs.

Volume-targeted ventilatory support is more flexible, easier to learn, and easier to manage than pressure-targeted or time-cycled ventilator support. All modern ventilators are capable of delivering adequate V_E and of varying the oxygen concentration (FiO_2) from 25% to 100%.

Most modern ventilators incorporate within a single unit, mechanisms that allow either volume-targeted or pressure-

Table 1: Comparison between volume-controlled (volume-targeted) and pressure-controlled (pressure-targeted) ventilation

Parameters	*Volume-targeted*	*Pressure-targeted*
Rate	Set or variable	Set or variable
Tidal volume (V_T)	Set	Variable
Peak airway pressure	Variable	Set
Peak alveolar pressure	Variable	Set
Peak flow	Set	Variable
I:E ratio	Variable	Set

Abbreviation: I:E, inspiration-expiration.

targeted ventilatory support, the use of PEEP, and the choice of several modes of ventilator support, detailed later. Adjustment of V_E, respiratory rates, flow rates, inspiratory-expiratory ratios are also possible. The ventilator is fitted with a series of alarms for better patient care, and can be fitted with modules that can monitor and display lung mechanics (compliance, airway resistance, wave-forms, flow-volume loops) and the end-tidal PCO_2.

From the clinical viewpoint, neither volume-targeted nor pressure-targeted ventilation offer a distinct advantage with regard to gas exchange, hemodynamic stability and pulmonary mechanics.

The major advantage of volume-targeted ventilator support is its ease of application, and the provision of a fixed V_T in spite of changing airway resistance or pulmonary compliance. The main advantage of pressure-cycled or pressure-targeted ventilation is that gas is delivered at a fixed preset pressure; if there is increased impedance to ventilation (either due to increased airways resistance or to a lowered pulmonary compliance), the V_T delivered falls. Overstretching of the alveoli with resulting volutrauma, barotraumas and biotrauma is thus prevented. Pressure-control ventilation may also be able to provide the high inspiratory flow demands of some critically ill patients.

For comparison between volume-controlled (volume-targeted) and pressure-controlled (pressure-targeted) ventilation see Table 1.

Management of Mechanical Ventilation

Initiating Ventilation—Basics of Initial Ventilator Set-up

There are a number of ventilator modes available to help ventilate a patient. We generally initiate ventilator support with volume-controlled or volume-targeted ventilation using the assist-control mode. In assist-control ventilation, the patient triggers the inspiration by a spontaneous effort which is enhanced by the ventilator. In this mode, if for some reason the patient fails to trigger the machine, the machine takes over, initiates inspiration and takes over full ventilatory support. Most patients with different respiratory problems can be adequately ventilated by the volume-targeted, assist control mode.

Tidal volume[6] The tidal volume for an individual patient should be set between 5 mL/kg and 10 mL/kg of body weight. Selection of V_T in a given patient is influenced by the nature of the disease, the approximate V_E requirement, pulmonary compliance, airway resistance, airway pressure, PaO_2 and $PaCO_2$.

Very low tidal volumes result in atelectasis, hypoventilation and hypoxemia. On the other hand, very high V_{Ts} can cause respiratory alkalosis, decrease cardiac output by reducing venous return and predispose to barotrauma, volutrauma and biotrauma. There is definite evidence that overstretch of alveolar walls through very large tidal volumes can induce lung injury.

In patients with normal lungs to start with (as in neuromuscular disease causing respiratory failure, CNS disease, coma, poisoning, and immediate postoperative conditions), the V_T is set at 10 mL/kg. In patients whose lungs are stiff because of abnormal respiratory mechanics (as in ALI, pneumonia) V_{Ts} are set at 5–7 mL/kg. A convenient algorithm is to start with 10 mL/kg, stabilize the patient and then progressively reduce the V_T to 5–7 mL/kg so that the plateau pressure does not exceed 30 cm H_2O.

Respiratory rate The rate is generally set between 10 and 14 breaths/minute, if the patient is clinically stable. Higher rates may be required (20–25/minute) in patients with stiff lungs [e.g. acute respiratory distress syndrome (ARDS)], so as to match the machine to the spontaneous breathing pattern of the patient. Lower rates may be necessary in chronic obstructive pulmonary disease (COPD) patients where V_E needs to be restricted. If the respiratory rate is too high, respiratory alkalosis, auto-PEEP and barotrauma can result. If too low, hypoventilation, hypoxemia and patient discomfort are observed.

Minute ventilation Minute ventilation is set according to the approximate ventilatory requirements of a patient and to start with is set at 5–10 L/minute. The V_E decided upon is also influenced by the nature of the disease and the altered respiratory mechanics for which ventilatory support is offered.

Inspiration-expiration ratio The I:E ratio to start with is set at 1:2 or 1:3 to allow sufficient time for expiration.

Oxygen concentration If the patient is hypoxic, the FiO_2 to start with should be 1.0. After 15–20 minutes, this is gradually reduced to a level, which allows a PaO_2 above or equal to 60 mm Hg, and O_2 saturation greater than or equal to 90%.

Inspiratory flow rate The inspiratory flow rate is usually set at 40–60 L/minute in volume-targeted ventilation. This can be increased to 60–100 L/minute in patients with high inspiratory flow demands. However, higher inspiratory flow rates would cause an increase in the peak inspiratory pressure. Lower flow rates can be used to decrease peak inspiratory pressure in patients who to start with have high peak inspiratory pressures (as in ARDS). Lowering inspiratory flow rates would increase inspiratory time, but decrease expiratory time—this could lead to air trapping, auto-PEEP, patient discomfort and barotrauma.

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Box 3: Common problems encountered during initiation of ventilator support

A. Difficulty in synchronizing patient's respiration with the ventilator—
   - Reassure patient and use tranquillizers (diazepam 5–10 mg IV)
   - Use adequate alveolar minute ventilation to maintain $PaCO_2$ at 35–40 mm Hg
   - Use high FiO_2 temporarily to ensure there is no hypoxia
   - Increase V_T and RR beyond patient's spontaneous rate. Once patient is taken over by machine, setting gradually lowered to desired values
   - Recognize and treat other factors contributing to 'clash' between machine and patient
   - If in spite of above measures asynchrony between patient and machine persists (as in patients with severe parenchymal disease producing stiff lungs), sedate and depress respiration by 2–4 mg IV morphine, or IV diazepam or IV midazolam, IV fentanyl or IV propofol or induce neuromuscular paralysis

B. Other problems—
   - Malposition of endotracheal tube
   - Aspiration of stomach contents
   - Hypotension

Abbreviations: IV, intravenous; RR, respiratory rate, V_T, tidal volume.

Positive End-Expiratory Pressure[7]

Positive-end expiratory pressure (PEEP) may need to be used if the O_2 saturation is less than 90% on an FiO_2 greater than 0.5 (see subsequent section on PEEP).

It needs to be stressed that the V_T, respiratory rate, V_E, I:E ratio and inspiratory flow rates are so adjusted as to enable good exchange of gases and yet maintain plateau pressure less than or equal to 30 cm H_2O. This lung protection strategy minimizes the risk of barotrauma and volutrauma.

All alarms on the ventilator provided both for patient safety and as indicators of proper functioning of the ventilator should be activated—in particular, the high pressure, low pressure alarm and the apnea alarm.

PROBLEMS AT INITIATION OF VENTILATOR SUPPORT (BOX 3)[8]

The major and the most common problem is difficulty in synchronizing the patient's respiration with the ventilator. In an unconscious or apneic patient this presents no difficulty.

The problem is also easily surmountable in patients with respiratory failure due to poisoning, neuromuscular disease, or other CNS problems. The following points are helpful in management—

- Allay anxiety and fright in the patient by explaining the situation in a gentle and confident manner, and by the use of a tranquillizer. Diazepam, 5–10 mg intravenously is of great help.
- The most common cause of difficulty in synchronizing is inadequate alveolar V_E. The V_E selected should result in a $PaCO_2$ between 35 mm Hg and 40 mm Hg. Ordinarily a V_T of 10 mL/kg with a respiratory rate of 12–15/minute is adequate. However, many patients with lung disease require higher V_E than that stated above.
- If the patient continuously clashes with what appear to be reasonable ventilator settings, it is advisable to proceed as follows—
  - Use a high FiO_2 temporarily to ensure that there is no hypoxia—this can be easily checked by noting the oxygen saturation on the pulse oximeter.
  - If a very strong respiratory drive is responsible for asynchrony between the patient and the machine, the V_T is increased, and the respiratory rate increased to well beyond the patient's spontaneous rate. Once the patient is taken over by the machine, the settings are gradually lowered and modified to the desired values. Generally, if alveolar ventilation is adequate, and if other causes contributing to restlessness and increased respiratory drive are looked into and taken care of, the patient does not fight the machine and is relaxed. The only way to determine whether the alveolar ventilation is adequate is by monitoring the $PaCO_2$. A $PaCO_2$ above 45 mm Hg denotes alveolar hypoventilation; that below 35 mm Hg, alveolar hyperventilation. Hyperventilation in the initial stages reduces the respiratory drive and helps the machine to take over. Once this is achieved V_E is adjusted so that the $PaCO_2$ is maintained around 35 mm Hg, and preferably not below 30 mm Hg.
  - In tachypneic patients with a strong respiratory drive, the patient's inspiratory flow rate is generally higher than the usual 40–60 L/minute set on the machine. Increasing the inspiratory flow rate appropriately, or decreasing the I:E ratio, prevents clashing and allows smoother ventilatory support in these patients.
  - Manual control of ventilation by using 100% oxygen for 5 minutes is a useful method for abolishing the patient's respiratory effort, by ensuring oxygenation, and proper alveolar ventilation.
  - Besides a strong respiratory drive chiefly related to altered mechanics of the lungs, there are other contributory factors, which increase the degree of clash between the machine and the patient. These may be present at the very outset, or may evolve during the critical care of a patient. They are briefly discussed later, and should be recognized and treated for more efficient ventilator support.
- Asynchrony between the machine and the patient may persist, however, in spite of appropriate ventilator settings, the use of corrective measures, and despite all attempts to match the machine to the patient. This generally happens in patients with severe parenchymal lung disease producing very stiff lungs, tachypnea and severe hypoxia. In many of these patients the spontaneous respiratory rate is greater than 40/minute. It is unwise to even attempt to

match the machine to this spontaneous respiratory rate. What is more, these patients are critically ill, often with multiorgan failure and cardiovascular instability. It is important that the respiratory muscles are rested in such circumstances. Effective ventilation can be achieved only by depressing respiration, or by inducing neuromuscular paralysis. The respiration can be depressed by the use of 2–4 mg morphine, or 0.2–0.4 mg buprenorphine intravenously, repeated as and when necessary. An alternative is to use 10 mg intravenous diazepam or 2–4 mg midazolam intravenously or an intravenous combination of midazolam and fentanyl, titrated to produce the desired effect. The main disadvantage of morphine is hypotension, which should be countered by vasopressors or by a volume load. In patients where morphine or a morphine derivative or diazepam or midazolam or fentanyl, is unsuitable or ineffective, particularly in ventilating patients with severe lung injury, it is necessary to use intravenous pancuronium or an intravenous bolus dose of vecuronium 0.08–0.1 mg/kg. After an intravenous bolus dose, vecuronium is given as a 0.8–1.2-μg/kg per minute continuous infusion, to induce neuromuscular paralysis and thereby abolish or sharply reduce spontaneous ventilatory support. Pancuronium is given as an intravenous bolus dose of 0.06–0.1 mg/kg and repeated as and when necessary to allow smooth takeover by the machine. It is unwise and often unnecessary to produce total paralysis with curare-like drugs.

Other important problems occurring within the first few minutes or hours of initiating ventilator support are—

- Malposition of the airways.
- Aspiration of stomach contents.
- Hypotension. These are dealt with at length under complications of ventilator support.

OBJECTIVES OF VENTILATOR SUPPORT

- Regulate gas exchange.
- Overcome mechanical problems.
- Increase lung volumes—in conditions in which the functional residual capacity (FRC) is reduced.

Regulate Gas Exchange

Oxygenation

- Most patients requiring ventilator support have uneven ventilation and disturbed ventilation-perfusion ratios. Only a small minority on ventilator support can be adequately oxygenated with room air or 20% oxygen; most require an increased concentration of oxygen in the inspired air.
  It is best to use an inspired oxygen concentration (FiO_2) sufficient to maintain O_2 saturation greater than or equal to 90% and a PaO_2 above or equal to 60 mm Hg. In severe lung disease, high oxygen concentrations are necessary; oxygen concentrations greater than 70% for a prolonged period are a hazard as they contribute to lung injury. In very severe lung injury, an FiO_2 of 100% may be necessary to prevent death from hypoxia. If this is indeed so, 100% oxygen should be used, notwithstanding the fear of oxygen toxicity.
- Use of PEEP. PEEP is indicated when the PaO_2 is below 60 mm Hg despite inspired oxygen concentrations exceeding 50%.

Carbon Dioxide Elimination and Regulation

The physiological dead space in patients with lung disease is often increased. The increase in dead space in relation to V_T may in fact be so large, that in some patients on ventilators 50–70% or even more of the V_T becomes dead space ventilation. It is therefore important to note the following points—

- It is impossible to predict the ventilation requirements of patients on ventilatory support as most patients have an increase in physiological dead space. Their ventilation requirements are invariably in considerable excess of that predicted by standard nomograms.
- The only certain way to ensure adequate ventilation is to measure the $PaCO_2$ and to adjust volume exchange so that the $PaCO_2$ is close to normal.
- It needs to be re-stressed that a disturbance in gas exchange may be as much due to a fault in the pulmonary circulation as to a fall in alveolar ventilation.
- Ventilator support can also be manipulated so as to purposely induce hyperventilation (with a low $PaCO_2$) in patients with raised intracranial pressure, or to purposely settle for hypoventilation (permissive hypercapnia) in certain clinical situations (ARDS and airways obstruction).

Overcome Mechanical Problems

Mechanical ventilation is of use to rest fatigued respiratory muscles, to overcome the abnormal mechanics of the thoracic cage in flail chest and to prevent or treat atelectasis.

Increase in Lung Volumes in Patients with a Low Functional Residual Capacity

Use of PEEP improves ventilation-perfusion ratios and reduces the right to left shunt within the lungs.

Summary of Ventilatory Patterns in Different Groups of Respiratory Diseases Requiring Ventilator Support

- In patients with normal lungs: V_T of 10 mL/ kg with respiratory rates between 10/minute and 14/minute, a flow rate of 40–60 L/minute, and an I:E ratio of 1:2 to 1:3 are recommended.
- Patients with trauma to the chest wall causing a flail chest, and often hematoma or injury to the lung.[9] These patients may need controlled ventilation for which sedation or neuromuscular paralysis becomes necessary. V_T of 10 mL/kg, with a respiratory rate between 12/minute and 14/minute are recommended. The V_E is adjusted to maintain a $PaCO_2$ between 30 mm Hg and 40 mm Hg.

- Acute hypoxemic respiratory failure due to severe lung disease, e.g. ALI, ARDS, pneumonia.[10] The principle is to avoid as far as possible high inflation pressure and to use small V_T of 5–7 mL/kg. In mild to moderately severe cases, smaller V_T of 6–8 mL/kg with a higher respiratory rate of 20–25/minute are used to match the patient's breathing pattern. The inspiratory flow rates are adjusted to between 40 L/minute and 60 L/minute. An increased FiO_2 and the use of PEEP are necessary. If adequate or efficient ventilation is not possible, particularly so in severely hypoxic, tachypneic, critically ill individuals, heavy sedation or even muscle paralysis with controlled ventilation becomes necessary, the principle again being not to exceed a plateau pressure of 30 cm H_2O as far as possible, even if this entails a rise in $PaCO_2$ (permissive hypercapnia). If pressure-controlled or pressure-targeted ventilator support is given to these patients, the peak inspiratory pressure should as far as possible not exceed 30 cm H_2O. PEEP is used in all patients. Inverse ratio ventilator support is occasionally tried when gas exchange remains unsatisfactory with the usual volume-targeted or pressure-targeted ventilatory support. The inverse ratio in our opinion should not be increased to higher than 1:1.
- Acute on chronic respiratory failure in patients with chronic airways obstruction. Small V_T of 6 mL/kg with a respiratory rate and V_E enough to allow a $PaCO_2$ between 45 mm Hg and 55 mm Hg are adequate. These patients are used to a high $PaCO_2$ and it is unwise to aim at a $PaCO_2$ of 40 mm Hg, as their $PaCO_2$ even under ordinary conditions is significantly elevated. Sedation or at times induced paralysis is often necessary for ventilator support to be effectively maintained. Moderately low inspiratory flow rates (50 L/minute), an I:E ratio of 1:3, and avoidance of high inflation pressure by using a low V_T is recommended. Hypoxia is countered by an appropriate increase in the FiO_2.
- Acute severe asthma. These patients also require low V_T (350–400 mL), and comparatively low V_E (often <5 L/minute) to prevent hyperinflation of the lungs. A rise in $PaCO_2$ does not matter as long as hypoxia is relieved by an appropriate increase in the FiO_2. Ventilation in these patients can at times prove extremely difficult.

Lung protection strategies (outlined in the Chapter Acute Lung Injury and Acute Respiratory Distress Syndrome) should always be kept in mind in the management of mechanical ventilator support. It is constant practice that allows the clinician to adjust ventilatory requirements to the need of each individual patient so as to allow adequate gas exchange and yet prevent as far as possible the hazards of mechanical ventilator support.

Three more points need to be stressed—

1. Hypovolemia contributes to poor gas exchange and accentuates or precipitates hypotension in patients on mechanical ventilation. It is therefore important to ensure normal circulatory volume, good pump function, a normal blood pressure and an adequate hemoglobin concentration.

Box 4: Conventional modes of ventilator support

- Controlled mode ventilation (CMV)
- Assist/Control mode (A/C)
- Pressure-controlled ventilation (PCV)
- Synchronized intermittent mandatory ventilation (SIMV)
- Pressure-support ventilation (PSV)
- Continuous positive airways pressure (CPAP)
- Inverse ratio ventilation (VC IRV) and (PC IRV)

2. Humidification of inspired gas, aseptic suction of secretions through the tracheobronchial tree at frequent intervals, and good chest physiotherapy are all vitally important. Good physiotherapy often spells the difference between life and death in critically ill patients on ventilator support.
3. Efficiently carried out mechanical ventilation can only ensure a satisfactory gas exchange. More often than not, a critically ill patient on ventilator support in the ICU has numerous other complications that pose potential hazards to life. Circulatory failure, renal dysfunction, bleeding, acid-base disturbances, overwhelming sepsis, and in our country, a poor nutritional state, singly or in combination with other factors, can be dangerous enough to cause death. Therefore, to concentrate solely on the correct and efficient working of a machine and on a single aspect of deranged physiology, constitutes bad medicine. An overall perspective should never be lost sight of in the management of a critically ill patient.

Modes of Invasive Ventilator Support[11]

The most common modes in use are volume-controlled ventilatory (VCV) mode,[11] pressure-controlled ventilatory (PCV) mode, synchronized intermittent mandatory ventilatory (SIMV) support, and pressure-support ventilation (PSV). These modes and the use of PEEP are considered to start with in this section, followed by a brief explanation of the more recent modes (Box 4).

It is very important for the clinician or the intensivist to be thoroughly familiar with the basic modes of ventilator support before attempting familiarity with the numerous other modes that modern ventilators are able to provide.

VOLUME-TARGETED SUPPORT

Controlled Mode Ventilation

In Controlled Mode Ventilation (CMV), the ventilator completely controls the patient's ventilation, delivering a set V_T (or a preset peak pressure) at a set frequency. It is indicated in individuals who are apneic, or in those with respiratory muscle paralysis. It is also indicated in patients who are heavily sedated or those paralyzed with neuromuscular agents so that ventilatory support is mandatory—a classic example of this situation is fulminant tetanus. Patients receiving CMV cannot increase their V_E voluntarily; their ventilator needs should

therefore be closely monitored, and changing needs should be met by suitable adjustments on the machine.

Assist/Control (A/C) Mode

This is the most commonly used mode. The machine delivers a preset volume (or pressure) in response to a patient-initiated breath. To prevent the patient from being totally dependent on triggered breaths, a back-up minimum respiratory rate is set. The requisite V_E can then be provided even if for some reason or the other the patient fails to trigger the machine. The main advantage of this mode is that the patient can increase his V_E by increasing his respiratory rate. The disadvantages include the production of respiratory alkalosis and of dynamic hyperinflation (particularly in COPD patients), if the machine is triggered too frequently, and the possibility of asynchrony between the ventilator and the patient. Initial ventilator settings are a V_E of 8–10 L/minute, respiratory rate at 10–14/minute, a sensitivity of –2 cm usually. If the patient triggers the machine too frequently, the sensitivity is set at –2 to –6 cm and the patient is sedated to reduce his respiratory drive. Most ventilators allow adjustment of the inspiratory flow rate or the I:E ratio, the inspiratory rise time, end-inspiratory pause time and the flow pattern during inspiration.

Pressure-Controlled Ventilation (PCV)[12]

In this mode, the maximum peak pressure is preset, so that the ventilator increases the pressure to this preset level with each inspiratory breath. The V_T obtained depends on the preset pressure (the higher the preset pressure, the higher the V_T), the stiffness of the lungs (greater the stiffness, the lower the V_T for a preset pressure) and resistance to airflow (the greater the resistance, the lower the V_T). The adjustable parameters are preset pressures delivered by the ventilator and the inspiratory time. The flow pattern is decelerating, in that the flow is high to start with, but decreases as the preset pressure is about to be reached.

Synchronized Intermittent Mandatory Ventilation[13]

In this mode, the ventilator delivers synchronized breaths at a set rate at either a preset V_T or a preset pressure, in addition to allowing the patient to breathe spontaneously.

The V_T and rate are determined by the patient. If for any reason, the patient does not breathe for a predetermined period, a machine breath is delivered. SIMV can be used with pressure support for spontaneous breaths. PEEP can be introduced in this mode, in which case the machine breaths will be combined with PEEP and the spontaneous ones with continuous positive airways pressure (CPAP). The advantages claimed for the SIMV mode are as follows—

- Decreased asynchrony with the machine and less sedation requirements.
- Less chances of hyperventilation as compared to the A/C mode.
- Greater patient comfort.

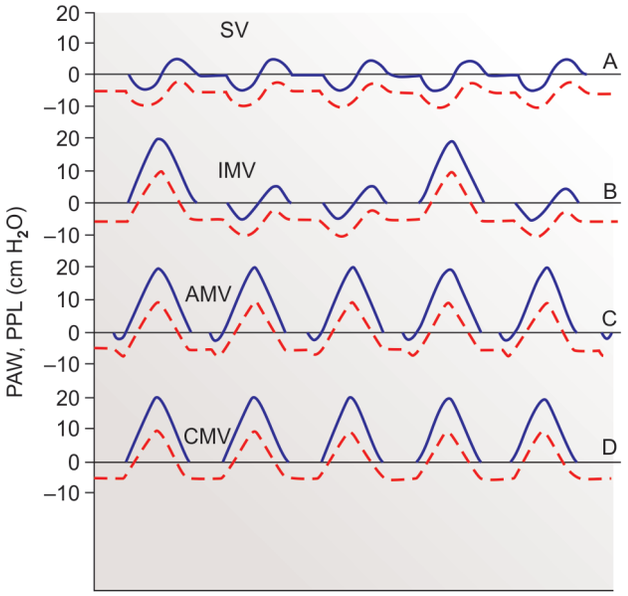

Fig. 1: Wave forms created by different modes of mechanical ventilation with positive pressure (B to D) compared with spontaneous ventilation (SV) (A). IMV, intermittent mechanical (mandatory) ventilation; AMV, assisted mechanical ventilation (or assist/control mode); CMV, controlled mechanical ventilation. Solid line, airway (PAW) or alveolar pressure; dashed line, pleural pressure (PPL)

Source: Luce JM, Tyler ML, Picrson DJ. Intensive Respiratory Care. Philadelphia: WB Saunders; 1984.

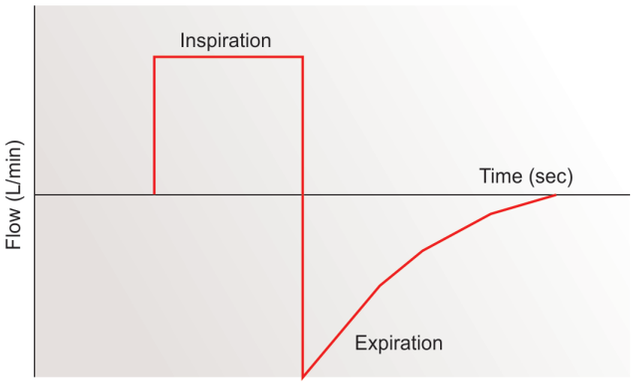

Fig. 2: A flow versus time curve for a mechanically volume targeted breath

- Continued use of respiratory muscles, which is believed to prevent respiratory muscle dysfunction.
- Reduced mean airway pressure even with the simultaneous use of PEEP, because many respiratory cycles are related to spontaneous breaths. This minimizes the cardiovascular effects of mechanical ventilation and is less likely to cause a fall in cardiac output or in arterial blood pressure.

In our opinion, the advantages ascribed to SIMV with or without PEEP are theoretical, and except in occasional instances, most patients are more comfortably and more satisfactorily ventilated with the A/C mode of ventilator support. In fact, the more ill the patient, greater the necessity to rest the respiratory muscles rather than exercise them.

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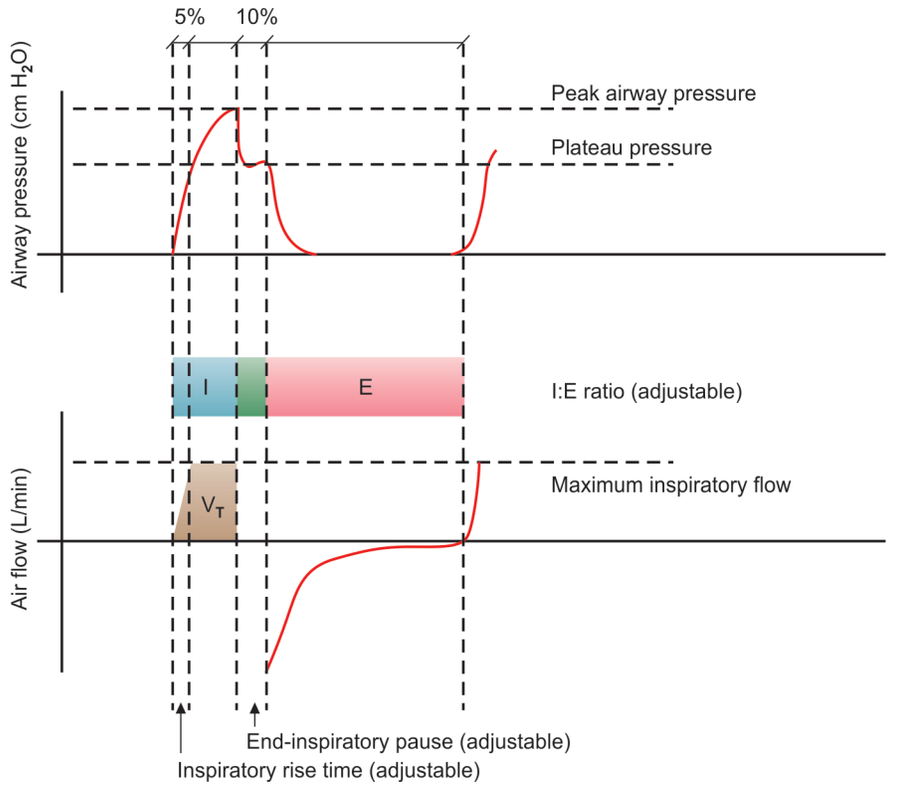

Fig. 3: Volume-targeted ventilation. Tidal volume is preset and the machine delivers the preset tidal volume regardless of change in compliance or airway resistance. Pressure rises during inspiration to peak inspiratory pressure (PIP). With a breath hold, the plateau pressure can be measured. Pressures fall back to baseline during expiration

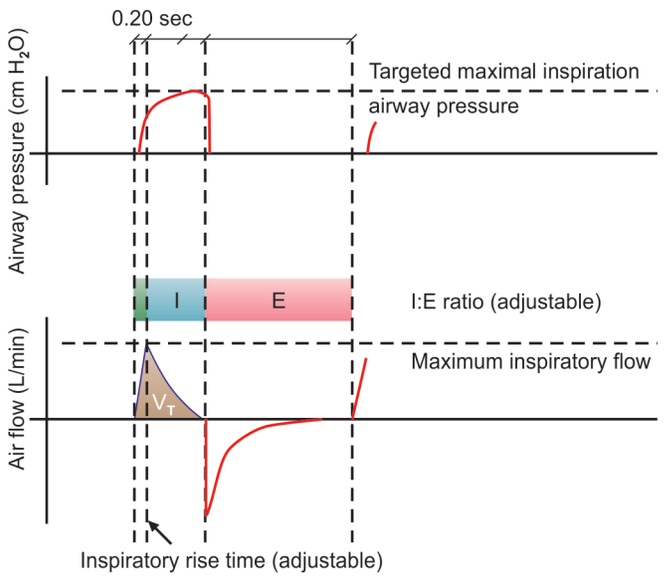

Fig. 4: Pressure targeted ventilation. The maximum inspiratory pressure is preset and the tidal volume will depend upon lung compliance and airway resistance. I:E ratio and the inspiratory rise time is adjustable

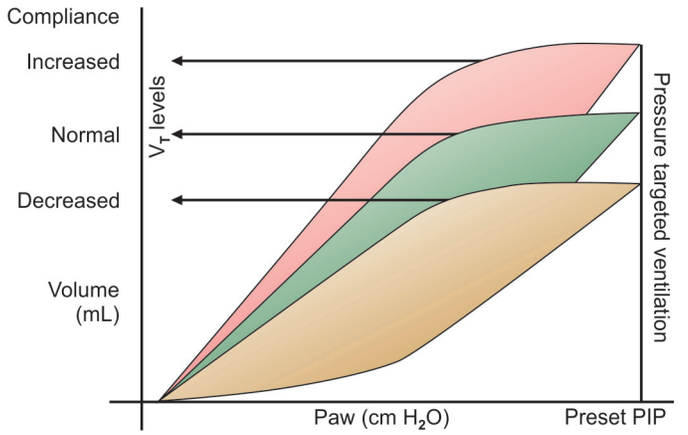

Fig. 5: Changes in the lung compliance in a patient receiving pressure targeted ventilation where the peak inspiratory pressure PIP is constant and the V, keeps changing. As dynamic compliance varies, so does the tidal volume

The VO_2 by overworked respiratory muscles can be as high as 15–40% of the total oxygen consumption and this is certainly undesirable. The SIMV mode cannot also respond to changes in the patient's condition, and therefore needs close monitoring.

The chief uses of this mode are stated below—

- In patients who develop hypotension while on the A/C mode or CMV mode with PEEP. The use of SIMV in such patients is associated with a lower mean airway pressure and this may restore cardiovascular instability.
- In patients on the A/C mode who develop respiratory alkalosis. This can be countered by either sedation or by changing to the SIMV mode.

- To prevent auto-PEEP in certain situations.
- In patients with respiratory failure and a bronchopleural fistula. In this situation, one would desire the lowest mean airway pressure that does not adversely affect ventilation and gas exchange, yet allows the bronchopleural fistula to heal and get sealed. Low V_T with increased respiratory rates to allow for adequate V_E, the avoidance of PEEP, and the use of the SIMV mode may be ideally suited to these patients. This should be combined with the lowest effective chest drainage tube suction.
- For weaning purposes (see Chapter Weaning from Ventilator Support).

Initial Setting

Settings to deliver a V_E of 6–10 L/minute or a preset pressure (sufficient to allow a V_E of 6–10 L/minute) with 10–12 mandatory breaths.

Pressure Support Ventilation[14]

In this mode a patient's inspiratory effort triggers a response from the ventilator. The ventilator delivers a preset positive pressure to the airways, reducing the work of breathing and helping in patient comfort. Once the predefined percentage of the maximal inspiratory flow is reached, the ventilator stops inspiration and opens the expiratory valve. The respiratory rate and inspiratory flow rate are determined by the patient. This mode cannot be used in an apneic patient or in one who lacks an adequate spontaneous respiratory drive. It is chiefly used in selected COPD patients and as a weaning procedure.

Initial Setting

Set a pressure of 10–12 cm of H_2O, ensuring a V_T of 7–10 mL/kg. The pressure support is gradually decreased to 5–7 cm H_2O provided an adequate V_T is maintained. Once this occurs, the patient can be weaned and allowed to breathe spontaneously.

Continuous Positive Airways Pressure

Continuous positive airways pressure (CPAP) is a mode of spontaneous breathing in which the airway pressure is maintained at levels greater than the ambient pressure throughout the entire respiratory cycle. A PEEP may be added as an adjunct to CPAP. All modern volume ventilators incorporate CPAP as a ventilatory mode. The ventilator does not provide any machine-generated breaths, but its humidification and alarm systems are available for use. Special CPAP systems without a ventilator are also available.

Inverse Ratio Ventilation

Inverse ratio ventilation can be volume-targeted or pressure targeted. Whereas the normal I:E ratio is 1:3 or 1:2, in inverse ratio ventilation the I:E ratio is 1:1 or even less. Ordinarily, one hesitates to go beyond 1:1. This is used in patients with ALI, ARDS, pneumonia, atelectasis, who show refractory hypoxemia (O_2 saturation <90% on an FiO_2 ≥60% on A/C mode in spite of suitable PEEP). In volume-controlled inverse ratio ventilation (VC-IRV), the inverse ratio of I:E is achieved by lowering inspiratory flow rate (and thereby lengthening inspiration) or by introducing a suitable end-inspiratory pause. The V_T is lowered sufficiently so as not to exceed a plateau pressure of 30 cm H_2O. In pressure-controlled IRV (PC-IRV), the I:E ratio is set to the desired level. The peak pressure should preferably not exceed 30 cm H_2O, or at most 35 cm H_2O. PEEP is used with both VC-IRV and PC-IRV.

The advantages attributed to IRV are better relief of hypoxemia and promotion of lung protection strategy that reduces the risk of both barotrauma and volutrauma.

Permissive Hypercapnia[15]

The principle behind this approach is to protect the lung from both volutrauma and barotrauma when using either volume targeted or pressure-targeted ventilatory support. Small tidal volume (5–7 mL/kg) are used in certain groups of patients in volume-targeted ventilatory support, so that plateau pressures do not exceed 30 cm H_2O. When pressure-targeted ventilator support is used, peak pressure is generally set to not more than 30 cm H_2O. This lung protection strategy can lead to hypoventilation and thereby hypercapnia. The hypercapnia is generally well tolerated by the patient and is permissible as an offshoot of the lung protection strategy stated above.

Use of Positive End-Expiratory Pressure[7]

The use of PEEP is a valuable adjunct to every mode of volume-targeted ventilatory support, pressure-targeted ventilator support, pressure-support ventilation and to the SIMV support.

The effects of PEEP and its complications are listed in Box 5.

Indications for Use of Positive End-Expiratory Pressure[7]

Positive end-expiratory pressure is indicated in patients with severe hypoxic respiratory failure who have poorly compliant lungs and a large degree of ventilation-perfusion mismatch so that hypoxia persists despite using an FiO_2 of 50–60% or more to ventilate the lungs. It is invariably indicated in patients with ALI, severe pneumonia, in patients with pulmonary edema who require ventilatory support and in hypoxemic respiratory failure due to flail chest and marked obesity. All these patients have a reduced FRC leading to alveolar and small airways collapse thereby causing a ventilation-perfusion mismatch with a right to left shunt within the lungs. In these patients, PEEP increases the FRC, opens up collapsed alveoli, particularly in the dependent lung regions, prevents derecruitment of opened alveoli during expiration, redistributes fluid within the alveoli and is believed to protect surfactant. The overall effect is to improve the ventilation-

Box 5: Physiological effects and complications of PEEP

Effects of PEEP

- *On lungs—*
  - Opening up of fluid-filled atelectatic alveoli, with increase in FRC and TLC
  - Decrease in shunt causing increase in PaO_2
  - Increase in V/Q units
  - Increase in dead space and V_D:V_T ratio
  - Increase in compliance up to a point; later fall in compliance
- On heart—
  - Decrease in cardiac output; this can decrease shunt, and thereby increase PaO_2. Thus rise in PaO_2 may also result from a fall in cardiac output, and not necessarily from improvement in lung function

Complications of PEEP

- Barotrauma—pneumothorax, pneumomediastinum, interstitial emphysema
- Fall in PaO_2 due to over distension of compliant alveoli, and increase in V/Q abnormalities
- Increase in intracranial pressure
- Water retention

Abbreviations: FRC, functional residual capacity; TLC, total lung capacity; V/Q, ventilation/perfusion; V_D, dead space; V_T, tidal volume.

Box 6: Practical guidelines for the use of PEEP

- PEEP only helps to counter hypoxia in acute hypoxemic respiratory failure due to lung injury; it does not alter the natural history of acute lung pathologies requiring ventilator support
- PEEP should not be used as a preventive measure, except after open heart surgery to prevent mediastinal bleeding, or to open up atelectatic segments chiefly present in the lower lobes
- It is not necessarily indicated if conventional ventilator support with FiO_2 of 50–60% maintains PaO_2 >60–65 mm Hg
- Start with PEEP levels of +5 cm H_2O, gauge effect, and then increase; do not exceed as far as possible levels of +15 cm H_2O in Indian patients as barotrauma invariably results
- Use the lowest PEEP that allows a PaO_2 of 60 mm Hg on FiO_2 <0.6; ascertain that the rise in PaO_2 following the use of PEEP is not associated with a fall in CO as this will lead to poor oxygen transport and poor tissue oxygenation
- If hypotension or decrease in CO is associated with use of PEEP, the PEEP level should be reduced, or even discontinued. The BP and CO are raised with volume load and/or inotropic support, and PEEP may then be better tolerated
- PEEP may rarely cause a fall in PaO_2—it then needs to be reduced, or even discontinued
- PEEP should be gradually tapered off, before discontinuing ventilator support

Abbreviations: PEEP, positive end-expiratory pressure; CO, cardiac output; BP, blood pressure.

perfusion mismatch, reduce the absolute right to left shunt (also termed the true venous admixture) within the lungs, thereby increasing PaO_2, O_2 saturation, so that need for high FiO_2 is reduced. The danger of oxygen toxicity caused by prolonged use of high FiO_2 in these patients is thus obviated. The prevention of derecruitment or collapse of alveoli during expiration with PEEP allows breathing to occur in the favorable range of the pressure volume curve, reducing the work of breathing. At one time PEEP was strictly contraindicated in patients with respiratory failure due to severe asthma or following an acute exacerbation of COPD requiring ventilator support. Many of these patients have dynamic hyperinflation of the lungs. The FRC is high and the alveolar pressure at the end of expiration exceeds atmospheric pressure, resulting in auto-PEEP or intrinsic PEEP. Also, because of dynamic hyperinflation this auto-PEEP progressively increases. A high auto-PEEP increases the inspiratory work of breathing and ultimately leads to respiratory muscle fatigue that can progress to respiratory arrest. The principle of ventilatory support is to use small tidal volumes with an I:E ratio of 1:3 and a rate preferably not more than 12–14/minute to help reduce dynamic hyperinflation. The application of extrinsic PEEP is also indicated in patients with severe airways obstruction who are on ventilatory support and develop a high auto-PEEP. The proper application of external PEEP will then counter the effect of auto-PEEP on the work of breathing, chiefly in relation to inspiratory effort. It is important however to set the level of extrinsic PEEP below that of the auto-PEEP observed in the patient.

In the past the main focus of attention in the use of PEEP was to improve oxygenation by reducing ventilation-perfusion mismatch and right to left shunt within the lungs. An equally important concept on the use of PEEP today is that it prevents the concertina-like opening and closing of alveoli during inspiration and expiration, keeps the alveoli open all through the respiratory cycle, thereby reducing the shear forces acting on the alveoli and hence reducing ventilator-induced injury (Box 6).

Selection of the Degree of Positive End-Expiratory Pressure Used

A variety of methods have been used to determine the optimal level of PEEP. In busy ICUs, the simplest, safest and the most practical method is to use the lowest level of PEEP, which maintains the PaO_2 equal to or above 60 mm Hg, on an FiO_2 equal to or less than 0.6. Other methods of selecting an optimum level of PEEP are described below.

Optimal Oxygenation

It is wrong to aim at an ever increasing PaO_2 by increasing the levels of PEEP. A high PEEP can cause an increasing rise in the PaO_2 and yet can result in a sharp drop in the cardiac output. This fall in cardiac output further reduces oxygen transport to the tissues, in spite of the increase in the PaO_2; this can have disastrous consequences.

Maximal Oxygen Transport

Adjusting the PEEP so as to obtain maximal oxygen transport (i.e. the product of arterial oxygen content and the cardiac output), takes the PaO_2, the hemoglobin and the cardiac output into consideration. Nevertheless, frequent measurements of cardiac output often pose problems in critically ill individuals.

Best Compliance

With the use of PEEP, the reduced FRC increases, and the compliance increases up to a point. If static compliance is measured with a graded increase in PEEP, a level of PEEP which produces an optimal increase in the compliance can be arrived at. Further increase in PEEP beyond this point now leads to a fall in static compliance pointing to overdistension of the alveoli. An optimal compliance produced by a particular level of PEEP in any particular patient, is generally associated with an optimal rise in the PaO_2.

Lowest Q_S/Q_T

As long as the level of PEEP does not significantly reduce the cardiac output, the optimal level of PEEP correlates with the lowest level of Q_S/Q_T. Many workers aim at reducing the shunt fraction to 15%, or aim at a PaO_2/FiO_2 ratio of 300 or more.

Lowest V_D/V_T and the Lowest $PaCO_2$-$PETCO_2$

The lowest V_D/V_T ratio and the lowest $PaCO_2$-$PETCO_2$ gradient are other parameters used by some workers to arrive at an optimal PEEP setting.

Complications of Positive End-Expiratory Pressure [7,16]

The three major complications are barotrauma, a fall in cardiac output, and at times a fall instead of the expected rise in PaO_2. PEEP used over a number of days, can result in an increase in intracranial tension, and to an increase in water retention, and a decrease in renal and portal blood flow.

Barotrauma

The risk of barotrauma depends on the end-inspiratory airway pressure and regional over inflation of parts of the lung. End-inspiratory pressure is a function of the V_T, the FRC, the inspiratory flow rate, the total compliance of the lungs, and the level of PEEP used. High V_T, high inspiratory flow rates and high levels of PEEP, in association with a reduced FRC and compliance, potentiate the risk of barotrauma. Even in severely diseased lungs, there are some regional areas which are more compliant than others. With high levels of PEEP, these alveoli get enlarged and overdistended, and have a lower recoil pressure than the smaller, poorly compliant alveoli. High alveolar pressure in such distended alveoli predisposes to rupture. On the other hand, the smaller, poorly compliant alveoli have a larger recoil pressure, and can therefore withstand high alveolar pressure and are less liable to rupture. Alveolar rupture can lead to interstitial emphysema, pneumothorax, mediastinal emphysema, and surgical emphysema of the soft tissues which may involve the neck, face and trunk. Pneumothorax on high levels of PEEP is a disaster which often leads to death.

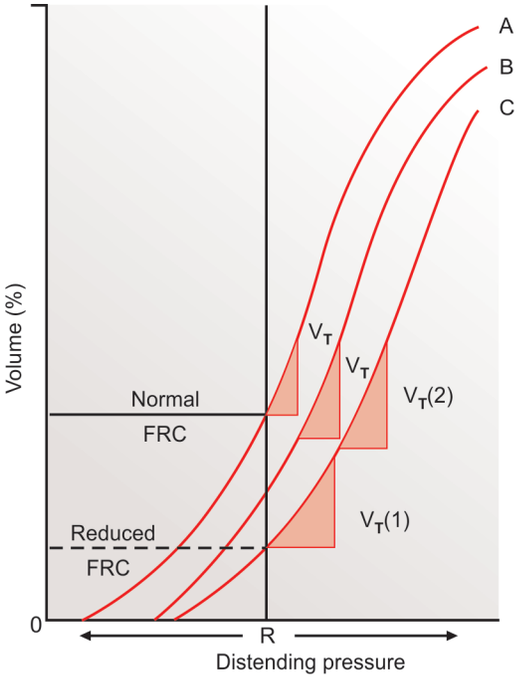

Fig. 6: Effect of positive end-expiratory pressure on functional residual capacity (FRC) in patients with reduced compliance, e.g. acute lung injury. Curve A represents a normal pressure-volume curve, wherein a relatively small distending pressure is required to achieve a given tidal volume (V_T). Curve C represents a pressure-volume curve in a patient with reduced compliance (as in acute lung injury) with decreased FRC. This is a more flattened curve and requires a greater distending pressure to achieve the same V_T(1). With the addition of PEEP, the FRC may be improved along the same abnormal compliance curve (2), or would shift to curve B, so that lesser distending pressure is required to achieve the same V_T but the absolute value of the distending pressure is still greater than that required for curve A

Fall in Cardiac Output

High levels of inflation pressure and PEEP are transmitted to the pleural space. The rise in the intrapleural and intrathoracic pressure leads to a fall in the venous return to the right heart, and a poor filling of the left heart due to a decrease in the transmural pressure across the left ventricular wall. Overinflation of the alveoli also increases the pulmonary vascular resistance with right heart strain, which further reduces the cardiac output. Also, right ventricular strain produces a shift of the interventricular septum to the left, thereby distorting and diminishing the size of the left ventricular cavity, and further impairing left ventricular filling and cardiac output. A sharp fall in the cardiac output leads to hypotension, poor oxygen transport, and inadequate tissue perfusion. A volume load together with dopamine support may be necessary in some patients to restore the cardiac output and oxygen transport to desired levels.

Table 2: Open lung procedure

Open lung and determine the opening pressure	Use Pressure Control Mode; rate 15/min I:E 1:1, PEEP 10–15 cm H_2O Raise PIP stepwise to 40–60 cm H_2O to open the lung. Allow 10–15 breaths for each stepwise increase in PIP Open lung—signified by a sharp sustained jump of PaO_2, PaO_2/FiO_2 and disproportionate increase in tidal volume. Note PIP for opening lung
Determine closing pressure	Lower PIP stepwise 2 cm at a time (allowing a few breaths at each reduction) till alveoli again start to close. This is signified by a sharp fall in PaO_2 and in tidal volume
Reopen lung	Reopen lung as described above
Now set PIP to just above closing pressure so that lung which has been opened is kept open	Stepwise reduce PIP to a level just above closing pressure to keep lung open. Check PaO_2, PaO_2/FiO_2 and tidal volume. Adjust respiratory rate for adequate ventilation

Abbreviations: PEEP, positive end-expiratory pressure; PIP, peak inflation pressure.

Fall in PaO_2

A paradoxical fall in the PaO_2 is sometimes observed with PEEP. This occurs when there are regional areas of normally compliant or over-compliant lung in patients with hypoxemic respiratory failure due to parenchymal lung disease. Overdistension of compliant alveoli leads to a decrease in the blood flow to these alveoli, and a shift of blood flow to the nonventilated, noncompliant areas of the lung. This causes a further increase in the shunt and a fall in the PaO_2. Ventilatory settings and PEEP levels should be adjusted to allow less distension of the compliant alveoli, and better distribution of inspired gas to the poorly compliant portions of the lungs.

Open Lung Concept[17]

The "Open lung concept" is being used in some critical care units in ALI and ARDS and in postoperative atelectasis (see Chapter Acute Lung Injury and Acute Respiratory Distress Syndrome). The principle behind this concept is to "open" the lung and keep it "open" with the least changes in pressure so as to minimize alveolar shear forces. This serves to improve gas exchange and serves as a lung protection mechanism by avoiding the concertina-like opening of the alveoli during inspiration and their collapse and closure during expiration. Sequential settings in a patient with ARDS on whom the open lung concept is used are given below.

- *Use pressure control* and set upper pressure limit to 50 cm H_2O. Set PEEP at 10–15 cm H_2O. Set pressure control level above PEEP to a value, which gives a V_T of 10–15 mL/ kg. Set respiratory rate at 15/minute. Inspiratory time 50% or I:E 1:1.
- *Determine opening pressure* Raise peak inspiratory pressure stepwise by 2 cm H_2O at a time, allowing 10–15 breaths at each stepwise increase, till the lung is fully "open". This generally requires a rise in the peak inspiratory pressure to 40–60 cm H_2O. The features that signify a fully "open" lung are a sudden and sustained jump of the PaO_2, so that the PaO_2/FiO_2 is greater than 400, and also the sharp disproportionate increase in V_T in relation to the stepwise increase in peak pressure.
- *Determine closing pressure of the lung* Decrease peak inspiratory pressure stepwise by 2 cm H_2O, allowing a few breaths for each setting to enable a stabilized reading. The closing pressure is that pressure at which the alveoli collapse or close. This is signified by an abrupt fall in the high PaO_2 and a sharp decline in V_T.
- *Reopen the lung fully* by repeating the steps outlined above.
- *Keep the lung open* Slowly, stepwise, reduce the peak inspiratory pressure once more to a level which is 1–2 cm above the closing pressure. Now the lung has been opened and is being kept open. The V_T should remain stable and the arterial blood gases good and constant.

Positive end-expiratory pressure is generally set at 10–15 cm H_2O. Some units prefer to set PEEP at higher levels of 15–25 cm H_2O. It is however not known if this high PEEP is necessary. Therefore, the same procedure as described above to determine ideal peak inspiratory pressure is now performed to find the lowest level of PEEP. After once again opening the lung, the peak inspiratory pressure and the PEEP are adjusted to just above closing pressure, so that the lungs remain open.

Avoid unnecessary ventilatory disconnects, or changes in ventilator settings. If ventilator disconnects occur or there is a change in lung condition to suggest further atelectasis, the whole procedure described above to reopen the lung and keep it open is repeated. Table 2 describes the stepwise open lung procedure.

NEWER MODES OF VENTILATOR SUPPORT

The conventional modes that provide ventilator support have been described above. They deliver a fixed, uniform, predetermined degree of assist without taking into account the variability of the breathing pattern present in different individuals in different situations and at different times in the same patient. Therefore, ideal synchrony between the patient and the ventilator is often absent. Asynchrony between the patient and ventilator can result in an increase in the workload. New technologies have therefore been developed that allow the ventilator to provide assistance in proportion to the patient's demand, which may vary from breath to breath. These newer modes of ventilator support are briefly considered below.

Airway Pressure Release Ventilation[18]

This ventilatory mode comprises CPAP that is intermittently released to allow a brief expiratory interval. The advantage is a lower mean alveolar pressure as compared to that during positive pressure ventilation. It has been used in patients with ARDS, and postoperatively in some patients, and has been found to be effective in providing adequate oxygenation.

Proportional Assist Ventilator

The ventilator in proportional assist ventilator (PAV) has the ability to sense every inspiratory effort breath-by-breath and adjust ventilator support accordingly. It does this by delivering positive pressure throughout inspiration in proportion to inspiratory airflow and volume generated by the patient. In conventional ventilatory modes, peak inspiratory pressure and V_T are relatively constant. In PAV, there is a direct constant relationship between the inspiratory effort of the patient and the peak inspiratory pressure generated by the ventilator from breath to breath. The V_T and peak inspiratory pressure are thus dependent variables. The PAV mode necessitates that the patient is capable of performing a portion of the respiratory work. It demands that the ventilator should be able to determine the elastance and resistance of the respiratory system in spontaneously breathing patients.

Pressure Regulated Volume Control and Volume Support

In the pressure regulated volume control mode a pressure-targeted ventilation is used to achieve a desired V_T. In the volume support mode a pressure support is given by the ventilator to achieve a predesigned V_T. This is done from breath to breath. The major concerns with both these assist modes is that if because of inspiratory respiratory demands (for example, fever or increased metabolism from any cause) there results an increased effort in breathing, the level of assistance offered by the ventilator will paradoxically decrease. Also, the machine delivers a predesigned V_T; however, in spontaneously breathing patients the V_T is not constant and may vary breath to breath.

Neurally-Adjusted Ventilatory Assist[19]

This mode uses the electrical activity of the diaphragm (EAdi) to control the ventilator. It is based on the concept that EAdi (triggered through the phrenic nerve) is representative of the overall neural respiratory effort both in timing and amplitude. In neurally adjusted ventilatory assist (NAVA), positive pressure exerted by the ventilator is in direct proportion to the amplitude of the EAdi, sensed by the ventilator. The patient's respiratory control mechanisms including feedback from various receptors adjust the EAdi; thereby regulating both V_T and the peak inspiratory pressure. NAVA has been tried out in specialized ICUs, and has been shown to enhance ventilator-patient synchrony, provide adequate gas exchange, unload respiratory muscles without alteration in circulatory hemodynamics, both during invasive and noninvasive ventilatory support. We have no experience with either the PAV or the NAVA ventilator modes and would rather wait for more clinical trials to define their optimum use.

Bilevel Positive Airway Pressure

In bilevel positive airway pressure (BiPAP) ventilation, two levels of continuous positive pressure are used, the patient being allowed to spontaneously breathe at both pressure levels. Assistance to spontaneous breathing can be given optimally at the low pressure level, high pressure level or at both levels. The change from low pressure level to high pressure level is co-ordinated by the patient's breathing effort. The BiPAP mode has its chief use in noninvasive ventilator support rather than in the invasive form.

High-Frequency Ventilation[17,20]

Several modes of high-frequency ventilation (HFV) have been employed. The basic feature in common is the use of a V_T which is smaller than the dead space volume. Gas exchange does not occur through convection as in conventional ventilatory modes, but by molecular diffusion, non-convective mixing, and by other mechanisms. The two important modes of HFV are high-frequency oscillatory ventilation and high-frequency jet ventilation. The advantages claimed for HFV include a decreased risk of barotrauma, and efficient gas exchange. This mode is believed to be best suited for healing of bronchopleural fistulae. Controlled trials, however, have shown no distinct benefit with this mode as compared to other conventional modes. The risk of complications is also significant.

Differential Lung Ventilation

Patients in respiratory failure due to severe asymmetrical lung disease may fail to be adequately ventilated by conventional ventilatory modes. In such patients adequate gas exchange can be provided by differential lung ventilation.

Clinical examples include patients with bronchopleural fistula, unilateral trauma, scoliosis or marked asymmetrical degree of parenchymal inflammatory disease in each lung (one lung being grossly affected and the other only slightly so). When there is a large difference in compliance, resistance or both parameters between the two lungs, a larger proportion of each tidal breath (using conventional ventilatory modes), is distributed to the comparatively unaffected lung. This results in a mismatching of ventilation and perfusion, an increase in the shunt, and poor gas exchange.

The initiation of differential lung ventilation requires the patient to be intubated with a double-lumen endotracheal tube (Carlen, Robert-Shaw, Univent, or Bronchocath). Different tidal volumes, flow rates, V_E, and if necessary even PEEP, are set for each lung. Differential lung ventilation can

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Box 7: Newer modes of ventilatory support

- Airway pressure release ventilation (APRV)
- Proportional assist ventilation (PAV)
- Pressure-regulated volume control (PRVC) and volume support (VS)
- Neurally adjusted ventilatory assist (NAVA)
- High frequency ventilation (HFV)
- Bilevel positive airway pressure (Bi PAP)
- Differential lung ventilation
- Extracorporeal membrane oxygenation (ECMO)

be through two asynchronous ventilators each with its own circuit and its own settings, or through two synchronized ventilators, which deliver tidal breaths to both lungs through two independent circuits. The V_T, FiO_2 and other ventilatory settings for each lung are independently adjustable.

Extracorporeal Membrane Oxygenation[21]

Extracorporeal membrane oxygenation has been dealt with in the Chapter Acute Lung Injury and Acute Respiratory Distress Syndrome to which the reader is referred.

The newer modes of ventilatory support are listed in Box 7.

COMPLICATIONS OF MECHANICAL VENTILATION[22]

Alveolar Hyperventilation

A $PaCO_2$ below 20 mm Hg can be dangerous. Respiratory alkalosis results in cramps, tetany, reduced cerebral blood flow and hypotension. Electrolyte disturbances characterized by a sudden shift of potassium from the extracellular to the cellular compartment can trigger dangerous arrhythmias like ventricular tachycardia, or ventricular fibrillation. Prolonged alveolar hyperventilation makes weaning difficult as the respiratory center gets used to a low arterial CO_2 tension, and cannot tolerate a rise of $PaCO_2$ to even normal levels.

Atelectasis

This may be of two kinds—

1. Segmental, lobar or even massive.
2. Diffuse airspace atelectasis.

Lobar or massive atelectasis is easy to detect clinically as well as on X-ray. It produces distress with a rise in the static compliance (a rise in both peak and plateau pressure is observed). A slipping of the endotracheal tube into the right main bronchus is an important cause of collapse of part or whole of the left lung.

Diffuse airspace atelectasis is characterized by a collapse of very many scattered alveoli in both lungs, so that both the clinical examination, and the chest X-ray are essentially normal. It is at times observed when tidal volumes less than 10 mL/kg are used to ventilate the lungs. The use of tidal volumes of 10 mL/kg is the best prophylactic measure for this complication. Diffuse airspace atelectasis is suspected when there is a fall in the compliance, with an increase in the alveolar-arterial oxygen gradient, and a normal chest X-ray. When due to an increase in the water content of the lungs, the condition can be corrected by the prompt use of a diuretic like furosemide.

Uneven Compliances within Different Areas of the Lung

These produce uneven distribution of inspired gas. When some areas of the lung are normal or over-compliant, while others show a marked decrease in compliance, the problem in mechanical ventilation is immense. Inspired gas overventilates the compliant lung, and often fails to open or ventilate the stiff or noncompliant parts of the lung. Overdistension of the compliant areas leads to increase in the physiological dead space, increasing Zone I conditions especially when large tidal volumes are used. The capillary perfusion in these areas is severely diminished, with blood being shunted to the less compliant, poorly ventilated areas. This produces an increased right-to-left shunt with a fall in the PaO_2. Lower tidal volumes with a judicious adjustment of PEEP are necessary, but the difficulties in providing adequate gas exchange are not always solved.

Auto-Positive End-Expiratory Pressure

An increase in PEEP occasionally occurs in patients on mechanical ventilation (auto-PEEP), even when PEEP is not used as an adjunct to ventilator support. Auto-PEEP (occult PEEP, intrinsic PEEP) is defined as an unintentional PEEP that occurs when a new inspiratory breath is delivered before expiration has ended, in patients on ventilator support. A progressively increasing auto-PEEP results in a dynamic hyperinflation of the lung, which is merely another expression for increasing air-trapping within the lung. Auto-PEEP and dynamic hyperinflation are most commonly seen in patients with COPD, where narrowed obstructed airways lead to prolonged expiration and air trapping. Other factors that predispose to the occurrence of auto-PEEP are—

- V_E equal to or greater than 10 L/minute.
- Patients over 60 years of age.
- Use of a small-sized endotracheal tube.
- Increase in V_T especially in patients with COPD.
- Increase in compliance.
- Increase in respiratory rate with increase in risk of air trapping, particularly when inspiratory time equals expiratory time.
- Reduced inspiratory flow rate with shorter expiratory time.

Measurement of Auto-PEEP

During normal mechanical ventilation, the auto-PEEP present in the patient's lungs at end-expiration is not registered on the ventilator manometer, as in most ventilators pressures during exhalation are measured internally on the inspiratory side of the machine. Also normally, the expiratory valve is open to the

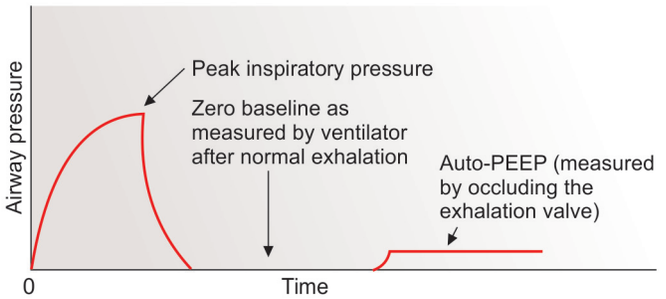

Fig. 7: The airway pressures (peak and plateau) during a positive pressure breath. Pressurizes during inspiration to peak inspiratory pressure (PIP). With a breath hold, the plateau pressure can be measured. Pressures fall back to baseline during expiration

Source: Pilbeam SP. Mechanical Ventilation, Physiological and Clinical Applications. Mosby: Mosby Year Book, MO® Elsevier; 1992.

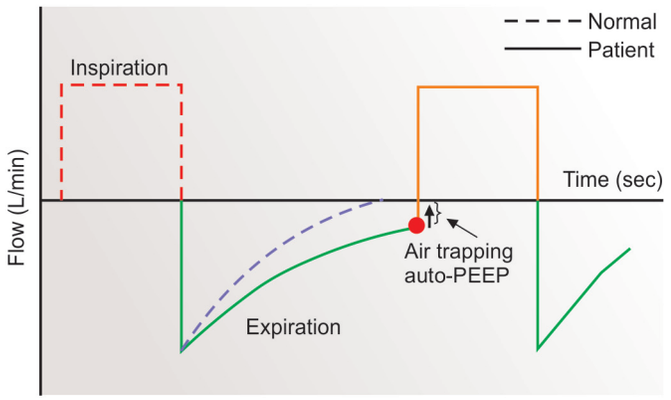

Fig. 8: Air trapping or auto-PEEP. Normally, expiratory flow returns to the baseline prior to the next breath. In the event that the expiratory flow does not return to the baseline and the subsequent inspiration begins below the baseline, auto-PEEP is present

atmosphere during exhalation. Auto-PEEP can be measured by occluding the expiratory limb of the circuit just before the next positive pressure breath. When the exhalation valve is occluded, the manometer measures the pressure in the patient's airway as the pressure equilibrates with the circuit. This method of measuring auto-PEEP requires a quiet patient on controlled ventilation.

Some ventilators like the Siemens Servo 900C and the Ohmeda Advent have end-expiration pause buttons or controls. They are microprocessor ventilators that can time the closing of the exhalation valve. They close this valve just before the next positive breath is due, delay the next breath, and then measure the pressure in the circuit.

Effects of Auto-PEEP

Effects of auto-PEEP are the same as those of PEEP used on purpose as an adjunct to ventilatory support. Deleterious effects include barotrauma, hypotension and a fall in PaO_2.

Methods of Reducing Auto-PEEP

Auto-PEEP can be reduced by the use of—

- Higher inspiratory flow rates, thereby shortening the inspiratory time and allowing longer time for expiration.
- Increased expiratory time by setting a smaller V_T and reduced respiratory rates.
- Low-resistance exhalation valves and large-bore endotracheal tubes to reduce air trapping.
- Low compressible volume ventilator patient circuit.

It must be mentioned that the occurrence of auto-PEEP is not confined to patients on ventilator support. It is frequently observed in spontaneously breathing patients who have severe airways obstruction that leads to air-trapping.

Infection

Nosocomial infection is an important complication and the following preventive measures are enumerated below—

- Cleanliness in the patient's room with scrupulous attention to avoiding cross-infection. Washing hands prior to examining the patient is important.
- Care of the tracheostomy wound—spraying the wound with an antibiotic spray is useful.
- Aseptic suction of secretions through the tracheostomy/endotracheal tube—should be done.
- Meticulous attention to prevention of atelectasis by physiotherapy and postural drainage. Prompt treatment of atelectasis and diffuse airspace collapse is mandatory.
- Frequent sterilization of humidifiers.
- Tracheostomy tubes should be changed every 4–7 days under aseptic conditions.
- Proper nutrition, oxygenation, and perfusion should be well maintained, so as to increase resistance to infection.

In patients on ventilator support, growth of Gram-negative organisms (chiefly pseudomonas strains and klebsiella) is frequently observed on culture of tracheal secretions. A positive culture by itself does not indicate infection, and does not warrant treatment (see Chapter Nosocomial Infections).

Hypotension

This is an important complication of mechanical ventilation. When it occurs soon after initiating ventilation, it is very likely to be related to the effects of the ventilator. In the presence of high inflation pressure, the use of PEEP, or in patients with over-compliant lungs as seen in emphysema, there may be a marked rise in intrapleural pressure. This reduces venous return and cardiac filling and induces a fall in blood pressure. Hypotension is often marked in hypovolemic patients. The treatment in such patients is to reduce inflation pressures, reduce or go off PEEP totally (if this has been used), and give a volume load to expand the circulating volume. Hypotension can also result from barotrauma, for example a pneumothorax induced by ventilator support. This may occur at the time of initiation of ventilator support or at a later period.

When hypotension occurs later during mechanical ventilation (the patient having been hemodynamically stable for several days), the cause is generally unrelated to the ventilator. Severe hypoxia and hypocapnia should be looked for, as they can induce a fall in blood pressure. If the blood gases are normal, hypotension may be due to shock, blood loss, fluid or electrolyte imbalance, sepsis, metabolic acidosis or poor pump function. Only if all these factors have been excluded, should the possibility of a ventilator-induced hypotension be considered.

Barotrauma, Volume Trauma and Biotrauma[23]

Barotrauma and volume trauma (volutrauma) are the most important and dreaded complications of mechanical ventilation. Probably, both high inflation pressure and high tidal volumes, particularly when PEEP is also used, contribute to barotrauma. It is generally the more compliant parts of the lungs, and not the poorly compliant areas, that are susceptible to barotrauma. Barotrauma classically takes the form of pneumothorax—tension pneumothorax occurs when high tidal volumes are used with high inflation pressures. Unless promptly recognized, it causes cardiorespiratory collapse and death. Interstitial emphysema, mediastinal emphysema and surgical emphysema of the soft tissues of the neck, spreading upward to the face and downward to the chest, may occur in the absence of pneumothorax.

A more subtle form of trauma to the alveolar walls can be caused by high tidal volumes (volume trauma or volutrauma). High tidal volumes are as important in producing alveolar damage as high alveolar pressures. The over-stretched alveolar walls are damaged, so that alveoli (even those which were reasonably normal), are now thickened, distorted and poorly compliant, thus adding to the overall stiffness and poor compliance of the lungs, and setting off a vicious cycle, which perpetuates respiratory failure to a point of no return. Over-stretch of alveoli with high tidal volumes is also believed to result in the production of cytokines that further injure the lung and perhaps also increase injury to other organs (biotrauma). The opening and closing of poorly compliant alveoli during inspiration and expiration results in shear forces that induce further lung injury (see Chapter Acute Lung Injury and Acute Lung Injury and Acute Respiratory Distress Syndrome).

Clashing with the Machine

This can occur at any time during mechanical ventilation, though it is most commonly observed during initiation of ventilator support. Clashing or fighting with the machine can be due to several causes, and each should be carefully evaluated prior to taking any decision on the management of the patient.

- Alveolar hypoventilation as stated earlier is an important cause; if present, it should be corrected by incr|easing the V_E.
- Obstructed tracheostomy/endotracheal tube or obstructed airways due to bronchospasm or mucus plugging is an important cause of distress, leading to a clash with the machine. A rise in peak pressure, with a fall in the dynamic compliance and a marked difference between the peak and pause pressure should point to the above cause.
- Atelectasis, pneumonia and pneumothorax are very important causes of a clash with the machine. Distress and high peak pressure with a fall in the compliance are observed.
- Blood loss (as in bleeding within the gastrointestinal tract), shock from any cause, electrolyte imbalance, metabolic acidosis, high fever, pain, a distended bladder or colon, or a dilated stomach are other causes that aggravate difficulties in synchronization with the machine.
- A strong respiratory drive due to altered mechanics within diseased lungs may defy all efforts to match the machine to the patient. It is in this group that controlled ventilation after inducing neuromuscular paralysis or after depressing respiration with intravenous diazepam or morphine is mandatory.

Gastrointestinal Complications[24]

Gastric dilatation and paralytic ileus are observed at times, particularly at the start of mechanical ventilation. The cause is obscure. Treatment is through gastric aspiration via a nasogastric tube, stopping all oral feeds and using intravenous fluids till such time as gut motility returns. The maintenance of fluid and electrolyte balance in such patients is precarious. Hypokalemia tends to aggravate the ileus, and needs to be carefully corrected by potassium replacement through intravenous infusions. Oral feeds are resumed once the gut motility returns.

Gastrointestinal bleeding occasionally occurs as a complication in patients on ventilator support. This is due to acute erosive gastroduodenitis in critically ill patients, particularly in those receiving corticosteroids. GI bleeding is particularly common with acute on chronic respiratory failure secondary to infection in patients with chronic bronchitis. These patients generally have a well-marked acidosis. Antacids and H_2-receptor antagonists, or sucralfate help stop bleeding. At times, laser therapy or endoscopic cauterization of bleeding points may be necessary. The blood loss should be replaced by transfusions.

Water Retention

Patients on prolonged ventilator support may retain water even in the clinical absence of left heart failure, or of a rise in venous pressure. Increase in the water content of the lungs may cause some degree of pulmonary edema. This produces impaired gas exchange, and fluffy shadows in the lungs on a chest X-ray. The problem is managed by restricting fluids to 1,000 mL in 24 hours, and by the use of diuretics like furosemide (Box 8).

Box 8: Common complications encountered during mechanical ventilation

- Alveolar hyperventilation resulting in $PaCO_2$ <25 mm Hg. This causes respiratory alkalosis (with decreased cerebral blood flow, tetany, hypotension), shift in K^+ from extracellular to cellular compartment causing arrhythmias, difficulties in weaning
- Atelectasis—segmental, lobar or massive, diffuse airspace collapse
- Uneven compliances in different areas of the lung resulting in uneven distribution of inspired gas and difficulty in mechanical ventilation
- Occurrence of auto-PEEP
- Nosocomial infection
- Hypotension—initially ventilator-related due to high inflation pressure; later, usually unrelated to ventilator support
- Barotrauma/Volutrauma/Biotrauma—pneumothorax, pneumomediastinum, interstitial emphysema, damage to alveolar walls
- Clashing with the machine
- GI complications—paralytic ileus, gastric dilatation, GI bleeds
- Water retention

Abbreviation: PEEP, positive end-expiratory pressure.

Box 9: Indications for NIPPV

- Acute exacerbation of COPD
- Mild to moderate cardiogenic or non-cardiogenic pulmonary edema
- Community acquired pneumonia with acute respiratory failure
- AIDS with pneumocystis infection or any other infection
- Hypercapnic respiratory failure due to chronic airways obstruction
- Obesity hypoventilation syndrome

Abbreviations: NIPPV, noninvasive positive pressure ventilation; AIDS, acquired immune deficiency syndrome.

Box 10: Contraindications to NIPPV

- Respiratory arrest or need for immediate intubation
- Inability to protect the airway
- Presence of copious respiratory secretions
- Hemodynamic instability or persistent hypotension
- Persistent arrhythmia
- Inability to cooperate or tolerate either the nasal or facial mask
- Presence of facial injuries

Abbreviation: NIPPV, noninvasive positive pressure ventilation.

NONINVASIVE POSITIVE PRESSURE VENTILATION[25]

A number of critical care units attempt, in suitable patients, to offer ventilatory support through a nasal mask or through a fitting orofacial mask, rather than through an endotracheal tube.

The major advantage of noninvasive positive pressure ventilation (NIPPV) is the reduced incidence of nosocomial pneumonia and of other complications associated with endotracheal intubation. The use of NIPPV has been standard therapy in patients with obstructive sleep apnea and in many patients with central sleep apnea. Other indications for NIPPV in acute respiratory failure are as follows—

- Acute exacerbation of COPD; acute crisis in COPD from other causes.
- In some patients with mild to moderate cardiogenic or noncardiogenic pulmonary edema. The more severe forms need intubation and ventilatory support.
- Community-acquired pneumonia with acute respiratory failure.
- In AIDS with *Pneumocystis* infection or with other forms of disseminated pulmonary infection.
- Hypercapnic respiratory failure due to progressive chronic airways obstruction, or due to the obesity hypoventilation syndrome.
- Postoperative respiratory failure (chiefly due to atelectasis).

It is obvious that if NIPPV fails to effect efficient gas exchange, or cannot be tolerated by the patient, prompt intubation with ventilator support becomes necessary. Indications for NIPPV are listed in Box 9.

Noninvasive positive pressure ventilation is contraindicated under the following conditions (Box 10)—

- In patients with a respiratory arrest or need for immediate intubation.
- Inability to protect the airway.
- In the presence of copious respiratory secretions.
- Hemodynamic instability or persistent hypotension (systolic <90 mm Hg).
- Occurrence of dangerous or persistent arrhythmia.
- Inability to cooperate or tolerate either the nasal or facial mask.
- In the presence of facial injuries.

NIPPV is also occasionally used after extubation in patients with marginal weaning criteria. NIPPV offers a transition from intubation to spontaneous breathing.

Different modes of ventilator support have been used with NIPPV. These include volume assist/control, pressure control, pressure support and the CPAP modes.

The major danger with NIPPV is the risk of aspiration of gastric contents. It is the best not to exceed positive inspiratory peak pressures of 20–25 cm H_2O as gastric dilatation with fear of aspiration can become a major problem. The setting should allow a V_T of 7–10 mL/kg.

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Bilevel pressure ventilators (BiPAP machine) should generally be used for long-term or chronic application of NIPPV as in patients with obstructive sleep apnea or patients with chronic hypercapnic respiratory failure due to COPD. The expiratory positive airway pressure (EPAP) is set at 3–8 cm H_2O and the inspiratory airway pressure (IPAP) from +10 to +20 cm H_2O to provide effective ventilation. A backup assist rate should be set during sleep.

Respiratory Monitoring during Mechanical Ventilation[8]

Monitoring of respiratory mechanics is only possible during volume-controlled ventilation, a ventilatory mode perhaps most often used in most ICUs at least at the start of invasive ventilatory support. The discussion below is limited to patients on volume-preset ventilation. Determining respiratory mechanics at the start and during mechanical ventilation is an important and necessary aspect of ventilatory management. It is important to note the peak pressures, the pause pressures, the V_{Ts}, the PEEP, both extrinsic and intrinsic (if present), and to determine from these observations the dynamic compliance, static compliance and the resistance of the airway.

Airway Pressure and PEEP Measurement[8]

Measurements are reasonably accurate when the patient is relaxed (preferably sedated) on volume-preset ventilatory support. The inspiratory airway pressure (Paw) has three components–one, to overcome resistance of the airways during inspiration, the second, to overcome elastic recoil of the alveoli and expand them, the third, equal to end-expiratory alveolar pressure (PEEP) if this is present.

Paw = PR + Pstat + PEEP where Pstat = static elastic pressure
PR = resistive pressure component
Paw = $VI \times R + V_T \times E + PEEP$

where VI = inspiratory flow
R = resistance of airways
E = elastance of the airways

The individual components of Paw when separated provide significant diagnostic and therapeutic information. PEEP can be measured by the end-expiratory occlusion method. Most ventilators now provide an expiratory pause switch which allows a direct read-out of the PEEP. An error may creep into the measurement of intrinsic PEEP by this method if there is a leak around the endotracheal tubing or around the endotracheal tube cuff or when there is continuous nebulization with bronchodilators at the time of measurement, so that there is gas flow into the circuit, or if the patient is not completely taken over by the machine, and is not relaxed. Extrinsic PEEP is measured as set by the machine. Once PEEP has been measured the remainder of the airways pressure (ΔP = Ppeak – PEEP) can be apportioned between the pressure needed to overcome airways resistance (Pres) and pressure needed to overcome elastic recoil (Pes). This is done by stopping flow at end-inspiration and allowing the Paw to drop to a plateau level (Pplat).

The difference between the peak pressure and the plateau pressure is a measure of the airway resistance. The greater the difference between the peak pressure and the plateau pressure the greater the airways resistance.

If the inspiratory flow rate (VI) is 60 L/minute or 1 L/second the airways resistance during inspiration (Pres) is between 4 and 10 cm H_2O. A rise in airways resistance denoted by an increase in the difference between peak airway pressure and plateau pressure is observed with bronchospasm, obstruction of the large airways or mucus plugging of the bronchi, bronchioles and small airways. An increase in airways resistance (increased difference between the peak and plateau pressures) also occurs if there is obstruction of the endotracheal tube or tracheostomy tube or the trachea. In patients with bronchospasm the airways resistance may fall after nebulization with a bronchodilator and this is evinced by a narrowing of the gap between the peak pressure and the plateau pressure.

There now remains the need to determine the resistance offered by the elastic recoil of the lungs. This is indirectly determined by computing the compliance of the lung.

Dynamic compliance = Tidal volume/Peak pressure – PEEP (if present)
Static compliance = Tidal volume/Plateau pressure – PEEP (if present)
The normal compliance is about 70 mL/cm H_2O

A reduced static compliance means increased elastic recoil of the lungs, i.e. stiff lungs as in pulmonary fibrosis, pulmonary edema, areas of atelectasis, ALI and consolidation. Static compliance is also reduced when a patient on ventilator support develops a pneumothorax, collapsed lobe or lung or when there is increased stiffness of the chest wall or in the presence of abdominal distension.

A significant fall in compliance (the causes of which are listed above) will cause a sharp rise in both peak and pause pressures, pointing thereby to stiff lungs but no increase in the airways resistance (since there will be no increase in the difference between peak and pause pressure).

An increased compliance is observed in emphysema in which there is a loss of elastic recoil within the lungs. If the cause of ventilatory failure in a patient is undetermined at the time of intubation an assessment of the peak and plateau pressure, and of the compliance will help to determine the nature of the problem. A normal peak and plateau pressure in a patient intubated and ventilated for ventilatory failure should make the physician suspect an impaired central drive to breath or neuromuscular weakness as the underlying cause of ventilatory failure.

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CHAPTER 39

Weaning from Ventilator Support

INTRODUCTION

Patients on mechanical ventilation should be weaned from ventilator support and extubated at the appropriate time. An unnecessary delay in weaning increases the patients's risk of nosocomial infection, trauma to the airways, adverse effects of prolonged sedation, and health care costs. Yet premature weaning can lead to reintubation with the enhanced risk of nosocomial pneumonia, increased morbidity and mortality.

There are a number of patients who are electively intubated and mechanically ventilated for brief periods of time for reasons other than respiratory failure. These include those ventilated briefly after major surgery as an extension of intraoperative and postoperative surgical care, or those intubated for airway protection. An abrupt termination of ventilator support and often quick extubation is generally possible in such patients, if the following criteria are satisfied—

- The patient is awake, alert and can breathe well spontaneously. He should have a good "blast" through the endotracheal tube, and if needs be, his tidal volume (V_T) can be checked by connecting a spirometer to the endotracheal tube.
- The clinical reason for ventilatory support no longer exists, or has resolved.
- The airways are free of secretions through proper suction or spontaneous coughing, and the patient is capable of protecting the airways from aspiration.
- The patient's chest X-ray is normal, and shows no atelectasis or pulmonary shadowing.
- In patients ventilated after open heart surgery or following major surgical procedures, the arterial blood gases (ABGs) and arterial pH should be normal or near normal, both during ventilator support, and after discontinuing support.
- The patient should remain under intensive care so that respiratory care can be continued in the form of humidification of inspired gas, nebulization therapy, physiotherapy, and if necessary, reintroduction of ventilator support.

The weaning parameters stated below are generally not required to be followed in these patients. When however postoperative pulmonary complications produce respiratory failure, or the presence of infection, bleeding or other complications lead to an increasingly critical state, the decision to wean is necessarily delayed. Clinical considerations together with the respiratory parameters, discussed below, help to decide the appropriate time to commence weaning from ventilatory support in these patients.

Patients who require ventilator support for long periods of time, extending for weeks or even months, are not easy to wean. Prolonged mechanical ventilation is often necessary in severe or fulminant tetanus, prolonged severe acute respiratory distress syndrome (ARDS), neurological problems such as acute infections, polyneuritis, poliomyelitis and injury to the cervical chord. It is also often necessary in fulminant *Plasmodium falciparum* infections, in other fulminant tropical infections such as leptospirosis, in severe sepsis, septic shock, and in multiorgan failure from any cause. In a number of critically ill patients, elective intubation and ventilatory support is offered at a point in time when ABGs are not markedly deranged. The decision to wean such patients from ventilator support should first and foremost be a clinical one, based on clinical considerations. Parameters for weaning are useful, but they should support or supplement a clinical decision, and never be used as a substitute for it.

Table 1: Wean screen criteria used to identify patients ready for a trial of spontaneous breathing

Criteria	*Description*
Reversal of respiratory failure	Evidence for reversal of underlying cause of respiratory failure
Adequate oxygenation	PaO_2/FiO_2 ratio >150–200 PEEP ≤5–8 cm H_2O FiO_2 ≤40–50% pH ≥7.25
Hemodynamic stability	Absence of myocardial ischemic Absence of clinically significant hypotension No vasopressors; dopamine or dobutamine <5 µg/kg/min
Respiratory drive	Capability to initiate an inspiratory effort

Abbreviations: PaO_2, partial pressure of oxygen in the blood; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

CLINICAL CONSIDERATIONS TOWARDS THE INITIATION OF WEANING FROM VENTILATOR SUPPORT

As a general principle, mechanical ventilatory support can only be withdrawn when the reasons for initiating it are no longer present. This usually means that the underlying disease, whether it involves the lungs or not, has been cured or has markedly improved.

In 2008, the American College of Chest Physicians (ACCP) recommend (on the basis of a multi-society sponsored task force study) that every patient on ventilator support should be assessed each day with a "wean screen" to determine when the process of weaning should be initiated. The recommended wean screen is given in the Table 1.

We agree with this weaning screen (if one wishes to use this label). The parameters in this screen are invariably screened and carefully noted on an intensive care unit (ICU) round often more than once every day. We however feel that the recommended screen takes notice solely of the relevant parameters in the cardiorespiratory system, ignoring the fact that serious involvement of other organ systems (present in many critically ill individuals) may impinge on the function of the cardiorespiratory system. Ignoring the above fact leads to premature weaning, a relapse into cardiorespiratory dysfunction, necessitating reintubation with a return of ventilator support—procedures, which enhance morbidity, mortality and health costs.

Guidelines are important, and should be understood. Yet they should never be blindly followed; clinical consideration and clinical judgment should never be sacrificed at the altar of recommended guidelines when caring for an individual patient.

Besides cardiorespiratory parameters mentioned in the weaning screen, the following conditions should be carefully assessed before initiating weaning (Box 1).

Box 1: Clinical considerations for weaning patient from ventilator support

- Mechanical ventilator support should be withdrawn only when the underlying disorder (pulmonary or extra pulmonary) is completely resolved, or has improved markedly
- Patient should maintain normal arterial blood gases on FiO_2 of 0.4 (except in patients with COPD whose basal $PaCO_2$ values are raised and PaO_2 is around 60 mm Hg)
- There should be no significant pulmonary infection, pulmonary edema, atelectasis or airways obstruction
- Acid-base and electrolyte disturbances should be corrected prior to weaning
- The patient should generally be alert, cooperative and mentally prepared to be weaned; he must be hemodynamically stable and preferably off inotropic support
- General nutritional state and neuromuscular status must be clinically assessed as to whether patient can cope with work of breathing
- In presence of high fever, seizures, gastric dilatation, paralytic ileus, GI bleeds, hepatic or acute renal failure, weaning should not be attempted
- On T-tube breathing, there should be no significant change in pulse rate, BP, no tachypnea or respiratory distress, should maintain normal blood gases and a tidal volume of 5–7 mL/kg

Abbreviations: FiO_2, fraction of inspired oxygen; COPD, chronic obstructive pulmonary disease; BP, blood pressure; GI, gastrointestinal; PaO_2, partial pressure of oxygen in the blood; $PaCO_2$, partial pressure of carbon dioxide in the blood.

- Blood gases as stated in the screen should be satisfactory before initiating the weaning process. An important exception to this is patients with chronic airways obstruction who are being ventilated for acute on chronic respiratory failure. These patients are used to a partial pressure of oxygen in the blood (PaO_2) of ≤60 mm Hg and to a high partial pressure of carbon dioxide in the blood ($PaCO_2$) even under normal conditions.
- The lungs should be free of infection, major atelectasis or edema, as far as possible. Airways obstruction, either from mucus plugging or bronchospasm should be significantly relieved, as these factors significantly increase the work of breathing.
- Disturbances in acid-base balance should be corrected before weaning is commenced. Metabolic acidosis can increase the work of breathing significantly, while alkalosis can result in mental obtundation, and depress respiration.
- A clinical judgment should be made whether the patient in the immediate future can withstand or cope with the demands imposed by the work of breathing. The general nutritional state and the neuromuscular status should be given careful consideration. Poor nutrition, electrolyte abnormalities, hypomagnesemia, hypokalemia and hypophosphatemia lead to difficulties in weaning.

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Severely catabolic states like tetanus result in marked weight loss and loss of muscle mass in spite of providing a large caloric and protein intake. High carbohydrate diets lead to an increase in carbon dioxide production with increasing demands on ventilation, particularly in debilitated individuals, or in those with pre-existing lung disease. In such patients, less carbohydrates and more fats should be used for nutrition.

Patients with severe liver cell dysfunction, complications caused by renal failure, chronic alcoholics, and those who have weathered a prolonged critical illness, often pose great difficulties in weaning, chiefly because of their poor nutritional state, and their inability to cope with the work of breathing.

Even when cardiorespiratory parameters are satisfactory, weaning is frequently unsuccessful in the presence of severe multiorgan failure involving other organ systems.

- Ventilator support should be continued and weaning delayed in the presence of high fever, seizures, or when complications such as gastric dilatation, ileus, gastrointestinal bleeding, or acute renal failure exist.
- The patient should be awake, alert and cooperative, though there are exceptions to this consideration. The patient should also be prepared, indoctrinated and motivated to go off the ventilator.

PROCESS OF WEANING

Weaning is established in two stages—

1. To free the patient of mechanical ventilator support so that he or she breathes spontaneously through an artificial airway.
2. Extubation (removal of the artificial airway) of the patient.

Indices to Predict Weaning Outcome

Many respiratory indices have been proposed in order to predict weaning outcomes. These include—

- Assessment of ventilatory parameters (Box 2).
- Oxygenation and $PaCO_2$ levels.
- Respiratory muscle strength.
- Work of breathing.
- Central respiratory drive.
- Pattern of spontaneous breathing in relation to tidal volume (V_T) and respiratory rate (f or RR) or f/V_T.
- Peak expiratory flow rate >60 L/minute.

Yang and Tobin[1] studied the predictive power of several respiratory weaning indices and showed that the rapid shallow breathing index (f/V_T) had the best predictive value. The other indices listed above had relatively poor positive and negative predictive values. The f/V_T screening test has a high sensitivity and is useful to predict success in weaning when the test is positive (f/V_T <105) and failure to wean when the test is negative (f/V_T >105). However, it must be stressed that the f/V_T test though sensitive has a low specificity (i.e. there is a large proportion of weaning failure patients in whom the test is positive).

Box 2: Objective respiratory parameters for weaning

- Ventilatory parameters—
  - RR <30/min
  - V_E <8 L/min, and not >10 L/min
  - V_T of minimum 5–7 mL/kg
  - VC of minimum 800–1000 mL
  - Maximum inspiratory force > – 20 cm H_2O
  - V_D/V_T <0.6
  - Alveolar-arterial oxygen gradient on FiO_2 of 1 <250 mm Hg
- Arterial blood gases—
  - pH 7.35–7.45
  - PaO_2 70–100 mm Hg on FiO_2 of 0.4
  - $PaCO_2$ 35–45 mm Hg

Abbreviations: FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in the blood; $PaCO_2$, partial pressure of carbon dioxide in the blood; RR, respiratory rate; V_T, tidal volume; V_E, minute volume; VC, vital capacity; V_D, dead space.

METHODS OF WEANING

- In the past, the following methods were utilized—
  - Weaning through lowering the number of ventilator-assisted breaths in a patient on intermittent mandatory ventilation.
  - Weaning through gradually reducing the level of inspiratory pressure support in a patient on pressure support ventilation.
  - Keeping the patient "on" and "off"; ventilator support, and progressively increasing the "off" periods and reducing the "on" periods so that the patient breathes spontaneous first all through the day and ultimately all through the night.

    It is now accepted that weaning with intermittent mandatory ventilation (IMV), significantly delays removal of ventilator support.[2,3]
- The currently accepted weaning strategy to free the patient from mechanical ventilator support is to allow a daily spontaneous breathing trial through a T-tube during which the patient is observed for signs of respiratory failure (Table 2). If there is neither respiratory or cardiac distress, nor any evidence of respiratory failure over a period of 120 minutes, prompt successful extubation can generally be achieved. If the spontaneous breathing trial is unsuccessful, the patient is put back on the ventilator and the spontaneous breathing trial is repeated each successive day till the test is judged to be successful. The patient is then kept off mechanical ventilator support and in most cases is ready for extubation.

  In a multicenter randomized trial, Esteban and colleagues[3] compared four methods of weaning from mechanical ventilation and noted that patients managed with daily spontaneous breathing trials were extubated three times more quickly as those managed with pressure support.

  Ely and colleagues[4] showed that patients managed with a two-step weaning protocol including a daily wean screen

Table 2: Spontaneous breathing trial failure criteria

Criteria	*Description*
Increased work of breathing	• Respiratory rate >35/min or <8/min for at least 5 minutes • Two or more signs of respiratory distress, including tachycardia, bradycardia, accessory muscle use, abdominal paradox, diaphoresis or marked dyspnea
Inadequate oxygenation	• Saturation level of oxygen in hemoglobin (SaO_2) <88% for at least 5 minutes
Hemodynamic instability	• Acute cardiac dysrhythmia
Neurological instability	• Abrupt change in mental status

followed by a spontaneous breathing trial were extubated 1.5 days earlier than when managed with physician-directed weaning.

Esteban and colleagues[5] subsequently evaluated the effect of the duration of the spontaneous breathing trial in a randomized trial. They found that patients who were extubated after successfully completing a 30-minute trial of spontaneous breathing had similar reintubation rates to those who were not extubated until they completed a 120-minute trial. Even so, most intensivists use a 120-minute trial in patients who fail multiple daily spontaneous breathing trials, before proceeding to extubation.

❑ *Pressure-Support Ventilation (PSV)* This is the most common technique used to withdraw mechanical ventilator support when a patient repeatedly fails to pass the spontaneous breathing trial. During weaning, the patient's pressure support is reduced by 2–4 cm twice or thrice daily. If the patient tolerates and is comfortable with a pressure support of 5–8 cm without positive end-expiratory pressure (PEEP) he or she is given a spontaneous breathing trial for 120 minutes and if this is successful, then the patient is ready to be extubated.

When a patient is on PSV, it is important to ensure that there is neither asynchronous breathing nor an ineffective respiratory effort. High levels of pressure support should be avoided as this can lead to high tidal volumes and alkalosis causing inefficient triggering with ventilator-patient asynchrony. Clinical experience[2,3] suggests that the optimal initial levels of pressure support in PSV should be at a level that provide a respiratory rate of 25–30/minute.

❑ *Role of Noninvasive Ventilator Support* Non-invasive ventilator support has been used in three different scenarios—

1. If after successful extubation in a patient weaned off mechanical ventilation, the patient develops "de novo" respiratory failure after a lapse of time, the intensivist has two options—(A) to reintubate and reintroduce mechanical ventilation, or (B) to use noninvasive ventilator support to help tide over the crisis. Two studies[6,7] that have tried to assess the value of noninvasive ventilation (NIV) in the above setting suggest that the use of NIV is of no help. We feel that each patient should be assessed separately notwithstanding the result of these studies. If NIV is used, it should not be persisted with if there is no clear improvement of respiratory failure after a lapse of 4–6 hours. Reintubation and mechanical ventilator support should not be unduly delayed.
2. Noninvasive ventilation is at times used as a preventive measure in high risk patients who have been weaned and extubated. If the patient is considered to be a high risk for reintubation he or she is put on NIV immediately after the endotracheal tube has been removed. Patients who fall in this category are generally old feeble patients, patients who remain hypercapnic at the end of the weaning test, those who have persistent cardiac problems and those who have presented difficulty in weaning. Of the two studies[8,9] carried out one showed a reduction in extubation rate when NIV was given post-extubation and the other showed in addition a decrease in mortality.
3. Rarely NIV is used as a substitute for invasive mechanical ventilation in some patients with chronic respiratory failure who are difficult to wean and who really do not fully meet the weaning criteria. They refuse a tracheostomy or are at high risk for a tracheostomy. Weaning can be successful through NIV in some patients that fall into this category.[10,11]

Newer Modalities A number of newer weaning modalities have been tried with which we are unfamiliar. The use of closed loop PSV[12,13] is one such modality that provides continuous ventilator assistance to a patient's needs 24 hours a day. The above modality as also others in use are tried in the hope of reducing weaning trials compared to conventional methods.

Tracheostomy Tracheostomy becomes necessary if ventilator support is necessary for over 10–12 days. It has both advantages and disadvantages (see Chapter Airway Management).

Unsuccessful Weaning from the Ventilator

Perhaps the commonest reason is wrong judgment in deciding to wean the patient. This will happen if the intensivist is solely protocol driven and has ignored clinical considerations. Potentially reversible reasons for prolonged ventilator support are (Box 3)—

❑ Inadequate respiratory drive.
❑ Inability of the lungs to carry out gas exchange either because of infection, atelectasis, stiff lungs (very low compliance) or airways obstruction.
❑ Inspiratory muscle fatigue.
❑ Elevated diaphragm from a dilated stomach, marked ileus or a severely distended colon.
❑ Incipient undetected cardiac failure.

Box 3: Reasons for prolonged ventilation—"difficult to wean"

- Inadequate respiratory drive
- Inability of the lungs to carry out gas exchange either because of infection, atelectasis, stiff lungs (very low compliance) or airways obstruction
- Inspiratory muscle fatigue
- Elevated diaphragm from a dilated stomach, marked ileus or a severely distended colon
- Incipient undetected cardiac failure

Box 4: Causes of extubation failure

- Patient unable to protect the airway
- Difficulty in clearing secretions
- Excessive endotracheal secretions
- Mentally obtunded either due to neurological problems or to sedation
- Poor cough reflex
- Respiratory muscle fatigue
- Incipient often undetected cardiac failure
- Associated serious comorbid conditions

Extubation—Removal of the Artificial Airway

In a number of patients, extubation (removal of the artificial airway) is successful if the patients have passed the spontaneous breathing test for a period of 2 hours. This signifies total freedom from ventilator support. Nevertheless, there are situations where the patient may not need ventilatory support but still needs an artificial airway for a further length of time varying from hours to days. This is likely if the patient is unable to protect the airway, has difficulty clearing secretions or is mentally obtunded either due to neurological problems or to sedation. A normal or near normal mental status is important for successful weaning. Salam and colleagues[14] carried out a study on patients who were extubated after passing a spontaneous breathing trial. They found that patients who were unable to complete four simple tasks were more than four times likely to require reintubation as compared to patients who completed the tasks. A poor cough reflex, excessive endotracheal secretions are also features, which should prompt the intensivist to delay extubation even when the patient has passed the spontaneous breathing test.

Sedation, though important in the management of many patients in the ICU who are on ventilator support can result in obtundation so that both disconnecting the ventilator and/or extubation is delayed. Interruption of all sedation at the time a patient is given the spontaneous breathing trial (wake up and breathe) leads to both quicker release from ventilator support and quicker extubation. It has been observed that patients who were made to "wake up and breathe" were discharged earlier from the ICU. There was also a 14% absolute reduction in the risk of death in 1 year when the above policy was followed.[15]

Extubation Failure Extubation failure is defined as the reintroduction of ventilator support within 24–48 hours of extubation. The extubation failure rate is the number of patients requiring the reintroduction of mechanical ventilator support divided by the total number of extubated patients. It is important to realize that extubation failure is associated with a significant increase in patient mortality and morbidity (Box 4).[16-18] The underlying pathology in a patient with extubation failure may well influence outcome. Patients requiring reintubation because of respiratory failure had a mortality of 30% compared to a mortality of 7% in patients reintubated because of upper airways obstruction.

ROLE OF INSPIRATORY MUSCLE FATIGUE IN THE WEANING PROCESS

Inspiratory muscle fatigue is often responsible for a patient failing the spontaneous breathing trial. It is also an important reason for reintubation once the patient has been extubated. Inspiratory muscle fatigue should be suspected if the respiratory rate is >30–35/minute on disconnection from the ventilator, if the respiratory excursions are poor, if there are periods of spontaneous apnea or irregularity in the breathing pattern, or if there is paradoxical breathing. Not uncommonly the only manifestation of inspiratory muscle fatigue is a failed spontaneous breathing test.

We have given an evidence based protocol driven approach to weaning from mechanical ventilator support—both in relation to disconnecting the ventilator and extubation. To summarize, evidence presented in Western literature suggests that if the patient passes the weaning screen, he should be given a daily spontaneous breathing trial through a T-tube for 2 hours. If he passes this trial (in that he shows no respiratory or cardiovascular distress or failure) he is fit to go off ventilator support and in most cases fit to be extubated.

We now need to give a critical appreciation and add a few caveats to the above.

- A protocol driven weaning program if divorced from clinical judgment has a significant chance to fail. The weaning screen (as proposed by the ACCP) which takes into consideration just cardiorespiratory parameters is not sufficient for a correct judgment in the suitability of initiating the weaning process. The overall criticality of the patient in relation to other organ functions and other complications prevailing in a particular critically ill patient must be given due consideration before considering the patient fit for weaning.
- The evidence in relation to the spontaneous 120-minute breathing trial is from Western countries. There is no large prospective trial in India, leave aside a multi-centered

randomized trial. We need to gather our own evidence. There is a difference in ethnicity between the West and India and other South East Asian and African countries. More importantly there is in all probability a difference in the case-mix of patients on mechanical ventilator support in the ICUs of the West and the East. Also the case-mix in tertiary private hospitals in large metropolitan cities of India is different from the comparatively poor patient population in the ICUs of large government and municipal hospitals of these cities. It is important to accept the fact that the standard of intensive care both in relation to intensivists and particularly in relation to the nursing staff varies in the different ICUs in our country and also in other developing countries.

- We have noticed that in our ICU even when a patient has passed the 120-minute spontaneous breathing test, he may fail to breathe well after 6–10 hours, necessitating a return to ventilator support. The more critically ill the patient is or has been, the more frequently is this observed. A premature extubation would have certainly resulted in a reintubation in these patients with the added increase in morbidity and mortality.
- The nutritional state of many patients in our ICUs is often poor. Perhaps a 120-minute spontaneous breathing trial is too short for such patients.
- Evidence notwithstanding, the reintubation rates in the West are significant. Vallverdu et al.[19] in a study of 217 medical and surgical patients noted an overall reintubation rate of 15%, ranging from 36% in neurological patients to 0% in chronic obstructive pulmonary disease (COPD) patients. Data by Esteban and colleagues[5,20] show a reintubation rate of 13–19%. What would be the reintubation rate in our ICUs? We feel for various reasons (some of which are mentioned above) that it would be more than the rates reported in the West.
- The role of protocols in hastening the weaning process has been questioned. Krishnan and colleagues[21] in a prospective controlled trial in a closed medical ICU compared protocol based weaning to usual physician directed weaning and did not observe any improvement in clinical outcomes with protocols.
- The 2-hour spontaneous trial method of weaning invariably fails in patients who have been on ventilator support for several weeks or months. We have successfully managed to wean most of these patients by giving spontaneous breathing trial for progressively longer intervals so that hours off the machine are gradually increased. The patient is then first weaned off support during the day and then slowly weaned off support during the night. Pressure support breathing is of help in these patients. Spontaneous breathing trials should be started when the patient breathes comfortably through a tracheostomy collar or a T-tube with a pressure support of 10–15 cm of H_2O.

CONCLUSION

In conclusion, once the patient is judged (this is a clinical and judgmental decision) to be ready for weaning he should be given a daily spontaneous breathing trial for 120 minutes. On the day, he passes the trial a decision needs to be taken about extubation. Should it be immediate or should one wait for some hours or even a few more days. If the duration of ventilator support has been short (<10 days) and there is nothing to suggest any contraindications to extubation the patient should be extubated promptly but watched closely. In our conditions, the decision to extubate is not to be taken by the nursing staff but by the intensivist. We have seen disasters if this dictum is not followed.

If however there is any risk in prompt extubation (after a successful 120-minute spontaneous breath test), or if for any reason it is felt that though the patient has passed the spontaneous breathing test over 2 hours, he could well show cardiorespiratory distress later (this again is a judgmental decision), it is better to delay extubation than risk the possibility of a reintubation, as the latter in our opinion carries with it greater morbidity and mortality. Also if the airway is in place, the patient can be reintroduced to ventilator support if after a lapse of time he shows evidence of cardiorespiratory distress.

Patients who have received prolonged ventilator support extending for weeks or months need a different approach in weaning—a gradual withdrawal of ventilator support as has been stated in the last caveat.

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SECTION

10

Fluid and Electrolyte Disturbances in the Critically Ill

- Fluid and Electrolyte Disturbances in the Critically Ill

CHAPTER 40

Fluid and Electrolyte Disturbances in the Critically Ill

INTRODUCTION

Disturbances in fluid and electrolyte balance are frequently observed in critically ill patients under intensive care. They occur in a wide spectrum of diseases, are not confined to any particular field of medicine and are common following burns, trauma and major surgery. An essential prerequisite for the management of fluid and electrolyte disturbances in the critically ill is the knowledge of the basic physiology which regulates fluid and electrolyte balance. The kidneys play a crucial role in this balance and are of paramount importance in maintaining the homeostasis of the milieu interior in relation to water and electrolytes. They conserve sodium and water through several mechanisms: Hormonal mechanisms acting via the kidneys include the effects of the antidiuretic hormone, the renin-angiotensin system, aldosterone and the natriuretic hormone. The reader should refer to a standard textbook for a more detailed analysis on the physiology of this important subject.

APPROACH TO PROBLEMS IN FLUID AND ELECTROLYTE IMBALANCE

The conventional and easy method of evaluating disturbances in fluid and electrolyte balance is the frequent measurement of the concentration of serum electrolytes. It is crucial to remember that intracellular and extracellular electrolytes are normally constant, and that major shifts in and out of compartments can occur in disease with minimal changes in serum electrolytes. Again, it is very rare in clinical practice to have a disturbance confined to sodium balance per se; disturbances in water balance invariably accompany the latter. In fact, changes in plasma sodium concentration often are a pointer to disturbances in water balance. Finally, gross loss of sodium, potassium and water may exist in the body without any alteration in the plasma concentration of these electrolytes; if the fluid and electrolyte losses are in the same proportion as normally exist in extracellular fluid and plasma (i.e. if the fluid loss is isotonic with plasma).

An evaluation of fluid and electrolyte changes in disease demands a consideration of (1) the electrolyte concentration in plasma; (2) the volume of its distribution in the body; (3) the rate and quantity of water and electrolyte loss out of the body (as in vomiting and diarrhea) vis-à-vis the intake of water and electrolytes; (4) the movement of electrolytes and water in and out of each compartment; (5) the possible sequestration of electrolytes and water within the body (as in ascites and intestinal obstruction), which represents a loss of extracellular fluid.

NATURE OF FLUID CHANGES IN THE BODY

These disorders are best categorized as follows—

Disturbances of Volume

If isotonic fluid is lost from, or added to the body fluids, only a change in the volume of the extracellular fluid is observed. A loss of intestinal secretions thus leads to a loss of isotonic fluid and to a depletion of fluid within the extracellular compartment. As sodium, chloride and water that are lost are isotonic with plasma, the plasma concentration of sodium chloride remains unchanged. Fluid will not be transferred from the intracellular to the extracellular compartment as long as the osmolarity of the two remains the same. Addition of isotonic solution to the body fluids will result in a volume excess within the extracellular fluid compartment. However,

the concentrations of sodium and chloride in plasma remain unchanged, and there is no shift of water between the intracellular and extracellular fluid compartments.

Disturbances in Concentration

Disturbances in concentration produce a change in osmotic activity of the extracellular fluid (and the plasma). If water alone is lost from or added to the extracellular fluid, the concentration of osmotically active solutes in this compartment will change. Sodium is the most important osmotically active ion in the extracellular fluid. If the sodium concentration in the extracellular fluid falls, water will pass into the intracellular compartment till the osmolarity of both compartments is again equalized. If sodium concentration in the plasma rises, osmotic activity of the extracellular fluid compartment is increased, and water passes from the intracellular to the extracellular compartment so that osmotic equality between the two compartments is re-established.

Disturbances in Volume and Concentration

Volume and concentration abnormalities may both arise because of disease or from inappropriate parenteral fluid replacement therapy. A classic example is the association of a volume deficit together with a fall in serum sodium concentration that results from a massive loss of gastrointestinal fluid (causing a volume deficit), where fluid replacement is only through water (producing a fall in sodium concentration).

Disturbances in Composition

Concentrations of ions other than sodium can be altered within the extracellular fluid compartment without much change in the effective osmotic activity of the extracellular fluid. This produces a compositional change, which may be comparatively small when it involves an electrolyte like potassium, and yet has disastrous consequences (e.g. a rise in serum K^+ from 4 mEq/L to 8 mEq/L), if not promptly corrected. Compositional changes also involve disturbances in acid-base balance.

A combination of any of the disturbances stated above is often present in a critically ill patient.

This chapter now briefly describes volume changes, and then proceeds to describe disturbances in sodium concentration (hyponatremia and hypernatremia). It then describes compositional abnormalities characterized by changes in plasma potassium, calcium, magnesium and phosphate levels. The compositional changes characterized by acid-base disturbances in critically ill are dealt in the Chapter Acid-Base Disturbances in the Critically Ill.

VOLUME CHANGES

Volume deficit or excess is diagnosed by clinical examination. It is to be stressed that a severe volume deficit may exist with a normal, low or even high serum sodium level.

Volume Deficit

Extracellular fluid volume deficit with a decreased volume within the effective intravascular compartment characteristically occurs in vomiting, diarrhea, intestinal fistulae, nasogastric suction and in fluid loss following burns.

Other important causes include sequestration of fluid in soft tissue injuries and infections, intra-abdominal or retroperitoneal infection, peritonitis, and sequestration of fluid within the gut in ileus or in intestinal obstruction.

Renal salt and water loss can occur because of diuretics, renal disease or to adrenal insufficiency.

In the intensive care unit patient, the causes listed above are generally obvious. Less obvious causes include an unsuspected inadequate fluid intake, or fluid loss through excessive sweating as in high fever, hot humid temperature, and in diseases like tetanus. The extent of volume changes during hemodialysis, hemofiltration, and fluid loss from surgical incisions and wounds may also be underestimated.

Clinical Features

Early features of hypovolemia include tachycardia and postural hypotension (difference of 10–20 mm Hg in systolic arterial blood pressure between the supine and sitting postures). With increasing volume deficit and hypovolemia, there is increasing tachycardia, hypotension, collapsed peripheral and central veins with a lowered central venous pressure, and a lowered pulmonary capillary wedge pressure. The skin is cold and clammy, and the urine output is decreased. The urinary sodium is less than 10 mEq/L except in patients whose hypovolemia is related to salt and water loss via the kidneys (the urinary sodium in these patients is normal or increased).

Mental changes include anxiety, restlessness, followed by apathy, and dullness that may progress to drowsiness and coma. Poor tissue perfusion leads to accumulation of lactic acid with lactic acid acidosis. Multiple organ failure ultimately results from prolonged uncorrected hypovolemic shock.

Management

The first principle is to restore circulating volume through infusion of intravenous (IV) fluids. Once this is satisfactorily achieved, disturbances in electrolytes and acid-base balance if present need to be rectified. This is dealt with at length in the Chapter Acid-Base Disturbances in the Critically Ill.

Volume Excess

In the ICU patient, volume excess is often iatrogenic when the fluid intake has consistently exceeded the output. Excessive IV infusions of saline and blood transfusions are important causes of hypervolemia. Renal insufficiency, congestive heart failure, liver disease and other causes of sodium retention or excessive sodium administration can all produce increase in extracellular fluid content and hypervolemia.

A hypervolemic state is manifested by edema, and still later by ascites and pleural effusion. The neck veins are full, and pulmonary congestion may be obvious on clinical

examination. If cardiac function is normal, the circulation is hyperdynamic with tachycardia, a warm skin, a bounding pulse with an increase in the systolic pressure and the pulse pressure. The CVP is raised beyond 12 mm Hg, and the pulmonary capillary wedge pressure is often above 20 mm Hg in the presence of pulmonary edema.

In cases of moderate volume excess salt restriction, restriction of fluid intake, and the use of furosemide as a diuretic, will correct the problem. Fulminant pulmonary edema secondary to overhydration from overtransfusion of blood or fluids is more appropriately dealt with by phlebotomy in stages, so that the pulmonary capillary wedge pressure is reduced below 15 mm Hg.

It is worth remembering that in certain disease states there may be an increase in the volume in the extracellular compartment, associated with a decrease in the effective circulating blood volume. Advanced congestive heart failure and cirrhosis of the liver are classic examples of salt and water retention producing an increase in the extracellular volume, yet being terminally associated with a failing circulation. Suboptimal filling of the vascular space can occur due to a loss of fluid into other spaces as is seen in hypoalbuminemia, portal hypertension, and increased vascular permeability to solute and water.

HYPONATREMIA[1,2]

Hyponatremia is characterized by serum sodium below 135 mEq/L. Severe hyponatremia (Na <120 mEq/L) is fraught with danger and should be promptly treated. Hyponatremia is common in critical care medicine and is observed in diverse medical and surgical problems.

Hyponatremia *always signifies an excess of water relative to sodium in the extracellular (and intravascular) compartment*. A pseudohyponatremia may be observed in patients with extreme elevation of serum lipids or proteins, which causes an increase in plasma volume with consequent reduction in plasma sodium concentration. However, this increase in volume is in the nonaqueous phase, while the sodium is contained in the aqueous phase of plasma. Therefore, in these patients, hyponatremia is not associated with excess of water relative to sodium.

True hyponatremia (excess water in relation to sodium) can occur with a low, a normal or an expanded extracellular volume. It is important to make this assessment from the clinical background and the etiology responsible for hyponatremia. Hyponatremia may occur acutely, or may be slowly progressive or chronic. Acute hyponatremia from any cause, when marked, is life-threatening, and should be promptly evaluated and treated.

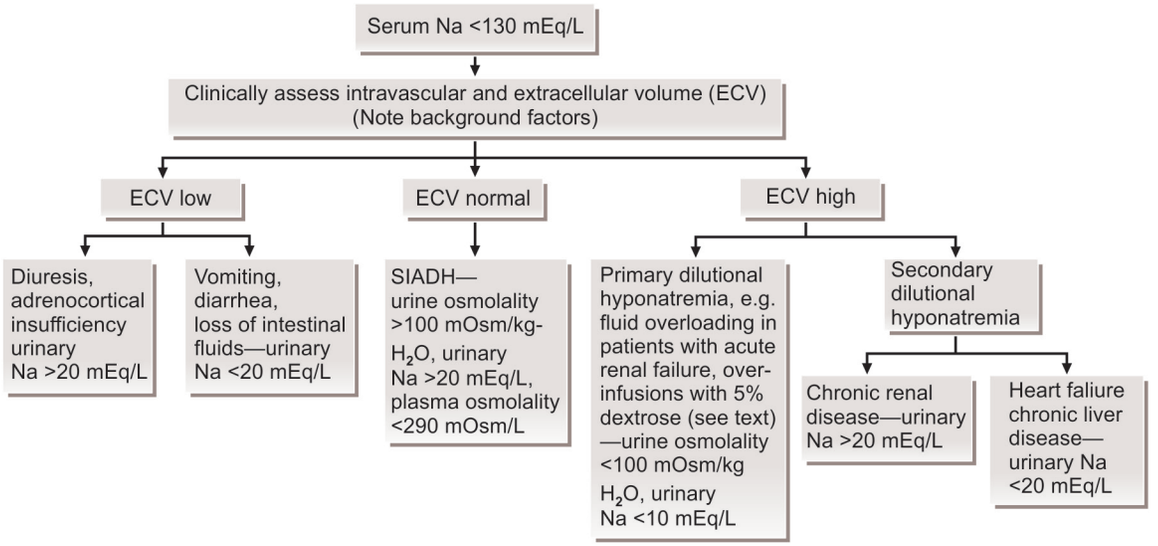
The causes of hyponatremia are considered below—

- *True salt and water depletion*—as in vomiting and diarrhea, particularly when fluid loss is partially replaced by dextrose or hypotonic solutions without adequate replacement of sodium and other electrolytes. The important causes of fluid and electrolyte loss have already been enumerated in the earlier subsection on "volume deficit". Hyponatremia due to loss of both fluid and electrolytes is associated with a contracted or low extracellular volume. The presence of a low intravascular volume is evident on clinical examination. Hyponatremia related to vomiting, diarrhea or loss of intestinal fluid is associated with a low urinary sodium (<20 mEq/L); that associated with sodium loss in the urine through diuresis or an adrenocortical insufficiency is associated with increased urinary sodium (>20 mEq/L).
- *Dilutional hyponatremia secondary to chronic heart failure, chronic liver or renal disease* These patients have an expanded extracellular volume, an increase in the total sodium content of the body, and are often waterlogged. The urinary sodium is less than 20 mEq/L in cardiac failure and in liver cell dysfunction, while it is often more than 20 mEq/L in chronic renal disease.
- *Primary dilutional hyponatremia* is generally evident from the history, e.g. overloading in acute renal failure, excessive infusions of 5% dextrose in postoperative patients, and compulsive water drinking in patients with diabetes insipidus who are on pitressin. Here again hyponatremia is associated with an increase in the intravascular volume and in the volume of the interstitial tissue compartment. In milder cases with this form of hyponatremia, clinical examination may not suggest an expanded extracellular volume, as about 5 liters of excess water need to be retained to produce definite pitting edema in an average-sized adult. The urine osmolality in these patients is decreased, and is always less than 100 mOsm/kg H_2O, with urinary sodium less than 10 mEq/L. The decreased urine osmolality distinguishes the above condition from the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) described below.
- *Syndrome of inappropriate secretion of antidiuretic hormone* In critical care medicine this is perhaps a frequent cause of hyponatremia, generally associated with euvolemia.[3] It is also observed after major surgery probably due to sustained nonosmotic release of vasopressin due to stress. The problem is compounded when the surgeon tries to increase the low urine output by IV infusion of glucose.

The diagnostic features of SIADH are hypo-osmolar hyponatremia, inappropriately concentrated urine (>100 mOsm/kg H_2O), clinical euvolemia and normal thyroid, adrenal, cardiac, hepatic and renal function. The urinary excretion of Na is more than 40 mEq/L in the face of a hypotonic plasma (<290 mOsm/kg). The important causes of SIADH seen in critical care medicine are given in Box 1.

In contrast to SIADH patients who excrete concentrated urine, euvolemic hyponatremic patients may present with maximally dilute urine (<100 mOsm/kg) in patients with psychogenic polydipsia or compulsive water drinking, the large consumption of water being in excess of the kidneys capacity to excrete free water, resulting in a dilutional

Flowchart 1: Algorithm for approach to hyponatremia



Box 1: Important causes of SIADH

Malignancies—
- Pharyngeal
- Genitourinary
- Pancreas
- Lymphomas

Pulmonary disorders—
- Bronchogenic carcinoma/Mesothelioma
- Fulminant pneumonia
- Pneumothorax
- Positive pressure ventilation
- Acute severe asthma

CNS disorders—
- Infections (abscess, meningitis, encephalitis)
- Trauma/intracranial hemorrhage
- Brain tumors
- Multiple sclerosis
- Acute psychosis

Drugs—
- Chlorpropamide
- Carbamazepine
- Clofibrate
- Narcotic-analgesics/NSAID
- Isoproterenol
- Nicotine
- Antimitotic drugs

hyponatremia.[4] Reset osmostatic is a chronic condition where the vasopressin osmoreceptors exhibit a lower threshold to the release of vasopressin. This is seen in quadriplegia, psychosis, tuberculosis and chronic malnutrition.[2]

Finally, adrenalcortial insufficiency and hypothyroidism are occasionally known to cause euvolemic hyponatremia.[2]

Essential hyponatremia (sick cell syndrome) This is observed in terminal stages of cardiac and liver cell failure, as also in the terminal stages of tuberculosis, malignancy, or other chronic illnesses.

It is important not only to diagnose hyponatremia, but also to determine its etiology and to determine from the clinical background whether it is associated with a contracted, increased or normal extracellular volume. The evaluation and approach to a hyponatremic patient is illustrated in Flowchart 1.

Clinical Features

The clinical picture of hyponatremia, when there is both a true salt and water depletion, is invariably dominated by features of fluid loss, which result in a reduced or contracted extracellular and intravascular volume. Dehydration and hypovolemic shock of varying degrees result (see Chapter Hypovolemic and Hemorrhagic Shock).

Salt depletion per se produces thirst, severe cramps in the legs, and later in the thighs and abdomen. Potassium depletion is also invariably present as an associated feature, and features of hypokalemia are therefore also often seen (see subsection on Hypokalemia). Fluid and electrolyte loss is also often associated with acid-base disturbances—metabolic alkalosis in vomiting, and metabolic acidosis in diarrhea. Lactic acid acidosis occurs with increasing impairment of tissue perfusion.

Symptoms due to hyponatremia depend on its severity and the rate at which it evolves. Symptoms generally occur with serum sodium less than 125 mEq/L and are chiefly due to water intoxication with edema of the brain cells. Patients may be lethargic, confused, stuporous or even comatose. In severe or rapidly evolving hyponatremia with serum Na less than 110 mEq/L, seizures and coma occur due to brain edema. The clinical picture at times, particularly in older patients, simulates a brainstem infarction or a subarachnoid hemorrhage with neck stiffness, stiffness of the limbs and coma. In a few cases, the diagnosis becomes first apparent on a cerebrospinal fluid examination, which shows a very low chloride content.

Management[5,6]

Hyponatremia due to Salt and Water Loss

In hyponatremia *due to both salt and water loss* causing a decreased intravascular volume, dehydration and hypovolemia are corrected by infusions of N saline (see Chapter Hypovolemic and Hemorrhagic Shock). As explained earlier, the flow rate is quicker through a large-sized catheter inserted in a peripheral vein. A central venous line helps to monitor the CVP and should be inserted if the patient is in shock. In severe shock, the simultaneous use of colloidal solutions (albumin or haemaccel) should be started to produce a more rapid expansion of the vascular compartment.

The total quantity of IV fluid depends on the degree of shock, the clinical history, an estimation of the rate and volume of fluid loss by carefully maintaining the output chart, and by the response to therapy. Thus, in a patient with a violent gastrointestinal infection, such as cholera, the fluid loss may amount to 500–1,500 mL/hour, and death results if the volume is not adequately replaced. Often in patients with a profuse fluid and electrolyte loss, 10–12 liters may need to be infused in the first 24 hours. The CVP should be maintained between 7 cm and 10 cm H_2O. Rapid infusions in patients with left heart disease or renal insufficiency can however trigger pulmonary edema even with a normal CVP. Clinical auscultation of the lung bases for basal crackles and a chest X-ray for pulmonary congestion aid in diagnosing this complication, and help in controlling the administration of IV fluids.

We invariably go by clinical considerations (this includes CVP monitoring) in adjusting the quantity, quality and rate of IV administration of infusions in hyponatremia associated with fluid and sodium loss. This is notwithstanding the formulae, which are given to help evaluate the degree of salt and water loss in different situations. Hyponatremia due to fluid and sodium loss is generally associated with hypokalemia and often associated with acid-base disturbances, which need to be corrected.

Severe Symptomatic Hyponatremia (Serum Na Less than 115 mEq/L)

Severe symptomatic hyponatremia with serum sodium less than 115 mEq/L deserves urgent correction as the mortality exceeds 50%. Management is guided by the clinical background. It is important to clinically assess whether hyponatremia is associated with a low extracellular volume (ECV), a normal or near normal ECV or an increased ECV.

Severe hyponatremia with a low ECV Hypertonic 3% saline is infused till the serum Na increases to about 125 mEq/L. The amount of sodium needed can be determined by estimating the sodium deficit.

Sodium deficit (mEq) = TBW × [125–serum Na of patient (in mEq/L)]

Where TBW is total body water.

The total body water (TBW) is taken as 60% of body weight, which in a 70 kg male amounts to 42 liters. It is to be noted (for reasons given below), that it is best not to increase serum sodium to more than 125 or at the most 130 mEq/L by the use of hypertonic saline.

Once the sodium deficit is calculated, the volume of 3% hypertonic saline to be infused is easy to determine as 1 mL of 3% hypertonic saline is equivalent to 1 mEq of sodium, 500 mL thereby roughly providing 500 mEq of sodium.

As mentioned earlier, volume replacement with isotonic saline to restore both vascular volume and the volume in the interstitial tissue compartment should be of prime importance in these patients.

Severe hyponatremia with a normal or near normal ECV This is best treated with restriction of water intake to 700 mL and the use of diuresis with furosemide. This is then followed by the use of isotonic saline. In severely symptomatic cases (and this is rare), hypertonic saline as described above may be administered.

Severe hyponatremia with an expanded ECV These patients are best treated with restriction of water intake to 700 mL and the use of furosemide diuresis. Hypertonic saline infusions invariably do harm to these patients. Water excess can be roughly estimated by the following equation—

Water Excess = TBW × (125/current plasma sodium) – 1

Where TBW is total body water.

Dangers of Rapid Correction of Hyponatremia: Osmotic Disequilibrium Syndrome[2,7,8]

Though severely symptomatic hyponatremia carries a mortality of over 50%, rapid correction of hyponatremia can in itself result in the dangerous complication of central pontine myelinolysis, now called the osmotic disequilibrium syndrome. Physiologically, in the presence of hypoosmolarity, water enters the brain cells; edema of the brain cells is responsible for obtundation, coma, seizures, temporal lobe herniation and death. The administration of hypertonic saline leads to withdrawal of this water from the brain cells. If the cellular dehydration is too rapid, it causes central pontine myelinolysis; myelinolysis can also occur in other parts of the brain. The clinical picture is typically characterized by obtundation progressing to coma, pupillary and ocular changes, with a progressive neurological deficient, such as pseudobulbar palsy and spastic quadriparesis. A magnetic resonance imaging of the brain confirms the diagnosis. This complication generally occurs 1–6 days after treatment. It has a poor prognosis and there is no effective treatment. To avoid this complication, the maximum rise in serum Na should not exceed 10 mEq/L in first 24 hours. Patients with acute hyponatremia (<48 hours) can tolerate a faster increase in sodium concentration. The rate of increase is sodium can be targeted at 1.5–2 mEq/hour so as to reach a goal of 120 mEq/L. Alcoholic and malnourished patients are at greater risk of developing central pontine myelinosis so that precautions stated above assume even greater importance.

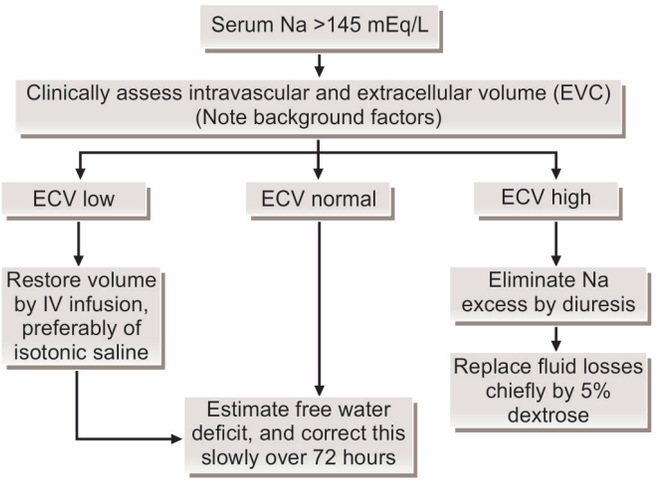
HYPERNATREMIA[2,9-11]

Hypernatremia exists when the serum sodium is in excess of 145 mEq/L. It means that there is an excess of sodium relative to water in the extracellular and vascular compartments. Hypernatremia, as is explained later, is invariably due to a massive depletion of water which relatively exceeds the depletion of sodium. In other words, most patients with hypernatremia are hypovolemic with a contracted extracellular volume. The increased osmolality in the extracellular fluid causes a shift of water from the intracellular to the extracellular compartment. Water loss from plasma is to an extent buffered. Massive loss of water is therefore necessary for significant hypernatremia to occur. The intracellular dehydration caused by hypernatremia chiefly affects the function of the brain cells as will be discussed later.

Hypernatremia observed in the ICU is (1) chiefly due to excessive loss of water relative to sodium; (2) occasionally it is due to very inadequate water intake in comatose or obtunded patients treated at home, or in old patients who are not looked after, or in those in whom thirst is either deficient or unsatisfied; (3) rarely it is iatrogenic and induced by excessive IV infusions of sodium bicarbonate (following cardiac arrest or to correct metabolic acidosis), or IV infusions of hypertonic saline used to correct hyponatremia.

- Water loss—
  - Through the gastrointestinal tract—gastric secretions are hypotonic to plasma; rarely unreplaced losses can lead to a hypernatremic, hypovolemic state.
  - Loss in hot climes can occur from excessive sweating. Large quantities of hypotonic fluid can be lost from the skin and to a lesser degree from the lungs. In burns, involving a large body surface area, hypernatremia is a common complication.
  - Loss of water from the kidneys in quantities sufficient to cause hypernatremia, occurs only in two conditions—uncontrolled diabetes, where water loss can be significantly greater than the sodium loss, and the solute diuresis, observed after IV mannitol and in uremic patients. Tube feeding in unconscious patients with feeds containing a high protein and low water content, can also produce hypernatremia in ICU patients. The products of protein catabolism following the use of such feeds, act as solutes producing a solute diuresis, more water being excreted than sodium.
- Excess of sodium—
  - We have rarely observed hypernatremia due to increased body sodium, because we carefully monitor the use of IV sodium bicarbonate, and use hypertonic saline only for the correction of acute symptomatic hyponatremia. When hypernatremia is due to an overall increase in the sodium content of the body, hypervolemia and an expanded extracellular compartment are always accompanying features.

Flowchart 2: Algorithm for management of hyperantremia


Serum Na >145 mEq/L
Clinically assess intravascular and extracellular volume (EVC) (Note background factors)
ECV low
ECV normal
ECV high
Restore volume by IV infusion, preferably of isotonic saline
Estimate free water deficit, and correct this slowly over 72 hours
Eliminate Na excess by diuresis
Replace fluid losses chiefly by 5% dextrose

Clinical Features

The clinical features produced by hypernatremia involve CNS dysfunction due to intracellular dehydration. To some extent the intracellular dehydration within the brain cells is reduced by a build-up of osmotically active solutes within the cells. Marked hypernatremia however results in a shift of water from the brain cells. This could cause petechial, intracerebral, subarachnoid or subdural bleeds, resulting in neurological deficits, and an obtunded or even comatose state.

A flowchart for the evaluation and management of a hypernatremic patient in the ICU is shown in Flowchart 2.

Management[12]

Hyperosmolar states (exactly like hypo-osmolar states), need gradual correction.

Hypovolemic hypernatremia (the most common form) is treated by first restoring volume by IV infusions, preferably of isotonic saline. It should be noted that hypovolemia though present, is not as marked as in hyponatremic states. This is probably because the hypertonicity within the plasma continues to draw fluid from the intracellular and interstitial tissue compartments, thereby preserving the blood volume to an extent. Once volume replacement is adequate (and this can be roughly gauged clinically), the water deficit relative to sodium is corrected. Hypotonic (e.g. half-strength saline) infusions are often advocated. However, as gradual correction is the aim of treatment, normal saline may be more suitable when plasma Na is more than 165 mEq/L. It is wise to take at least 72 hours to correct the water deficit, only about one-third of the excess of sodium concentration being reduced in the first 8 hours. Over-enthusiastic infusion of hypotonic solutions can lead to a rebound cerebral edema in place of the previous dehydration of nerve cells. Sudden shifts of water also enhance the tendency to cerebral hemorrhage. We have observed one patient who developed central pontine myelinolysis during correction of a hypernatremic state.

It is difficult to determine the exact free water deficit in hypernatremic patients. A method, which gives a rough estimate of free water deficit and which serves as a guide to fluid replacement is illustrated below.

For example, a 70 kg man has serum sodium of 170 mmoL/L, which needs to be lowered to 140 mmoL/L. The TBW is taken as 60% of the body weight, which in a 70 kg individual amounts to 42 liters. To reduce the plasma sodium, this volume needs to be increased to 170/140 × 42. This equals to 51 liters, which means that a positive balance of 9 liters is required. A slow replacement with isotonic saline, or both isotonic and hypotonic saline infusions over 4 days should restore plasma osmolality safely to normal limits. Infusions to correct hypernatremia should be monitored both clinically and by estimating the plasma electrolyte levels.

Hypervolemic hypernatremia is rarely encountered and is due to excessive infusion of sodium containing fluids, chiefly sodium bicarbonate. When due to infusions of sodium bicarbonate, if the bicarbonate solution contains 1 mEq Na/mL, then the excess of sodium due to sodium bicarbonate can be calculated thus—

$$\text{Sodium excess (mEq)} = 0.6 \times \text{wt. (kg)} \times (\text{Patient's serum Na-140})$$

The sodium excess is removed via the urine by diuresis, and the sodium concentration in the urine will give an approximate idea of the volume of urine required to be passed to eliminate the excess sodium. Thus, a sodium excess of 500 mEq with urine sodium of 100 mEq/L, would necessitate urine output of 5 L to excrete the excess sodium.

$$\text{Volume of urine to excrete excess sodium} = \frac{\text{Excess Na (mEq)}}{\text{Urinary Na (mEq / L)}}$$

Volume loss in the urine needs to be replaced mainly by 5% dextrose, else the excretion of hypotonic urine will cause a further rise in serum sodium.

Hyperosmolar nonketotic diabetic states Hyperosmolar hypernatremic nonketotic diabetic coma is dealt with as a separate entity in another chapter.

HYPERKALEMIA[13,14]

Hyperkalemia exists when the serum potassium (K^+) is above 5.5 mEq/L. Hyperkalemia is a dangerous potentially fatal condition. A rise of K^+ above 7 mEq/L is life-threatening and values above 10 mEq/L are incompatible with life.

Hyperkalemia in an ICU setting is due to:

- Release of K^+ from cells following injury: crush injuries, trauma, ischemic injury due to acute severe peripheral vascular disease are all conditions causing hyperkalemia.
- Uncontrolled diabetes even if associated with an overall K^+ deficit in the body may be associated with hyperkalemia due to shift of K^+ from the cells into the interstitial tissue and vascular compartments.
- Metabolic acidosis causes a shift of H^+ ions into cells, and a shift of K^+ ions out of the cells into the interstitial tissue compartment. Respiratory acidosis has little or no effect on serum K^+. Lactic acid acidosis has a lesser effect on cellular shifts in K^+ when compared to the acidosis of renal failure.
- Excessive K^+ intake particularly in patients with mild renal insufficiency can produce a dangerous rise in serum K^+ in critically ill patients. The routine, unchecked use of high concentrations of KCl orally in patients on a small dose of furosemide is dangerous and reprehensible, particularly in elderly patients with impaired renal function.
- Hyperkalemia is frequent when there is reduced renal excretion of K^+. This occurs in an ICU setting chiefly in patients with renal failure. Ordinarily the glomerular filtration rate should be as low as 10 mL/minute, or the urine output less than 1 L/24 hours for the serum K^+ to rise.[13] Acute renal failure, acute or chronic renal failure and the ingestion of a diet rich in K^+ by patients on hemodialysis for chronic renal failure, are perhaps the most frequent causes of hyperkalemia in an ICU setting.

Box 2: Important causes of hyperkalemia in an ICU setting

- Crush injuries, trauma, ischemic injury due to acute, severe peripheral vascular disease
- Uncontrolled diabetes mellitus
- Metabolic acidosis
- Excessive potassium intake, particularly in patients with renal insufficiency, or in those on hemodialysis
- Acute renal failure, or acute or chronic renal failure
- Use of angiotensin converting enzyme inhibitors in the treatment of hypertension, or of potassium-sparing diuretics like aldactone
- Rarer causes—interstitial nephritis, hyporenic hypoaldosteronism, adrenocortical insufficiency

An important cause of moderately severe hyperkalemia in an ICU setting is the use of angiotensin converting enzyme inhibitors in the treatment of hypertension, or the use of potassium-sparing diuretics like aldactone.

Interstitial nephritis and hyporenic hypoaldosteronism are comparatively rare causes, but can produce hyperkalemia without the presence of marked renal dysfunction.[13] Decreased potassium excretion via the kidneys due to adrenocortical insufficiency is also a rare cause of hyperkalemia in the ICU. The clinical picture in these patients, however, is not dominated by hyperkalemia.

The important causes of hyperkalemia in an ICU setting are listed in Box 2.

Clinical Features

The clinical features of hyperkalemia are characterized by muscle weakness and conduction disturbances. Muscle weakness is associated with hypotonia, areflexia, and may proceed to flaccid quadriparesis.

Bradycardia, junctional rhythms, various degrees of heart block and hypotension are observed with increasing K^+ levels.

Fig. 1: ECG changes in hyperkalemia. Note the slow idionodal rhythm with tall peaked T-waves progressing to an idioventricular rhythm with marked widening of the QRS complex. Note also the absence of P-waves

Death usually occurs from cardiac arrest. Electromechanical dissociation may be observed.

Electrocardiography Features (Fig. 1)

- The earliest manifestation of hyperkalemia is a peaking of the T-waves—this is often seen when the serum K^+ exceeds 5.5 mEq/L. Absence of peaked T-waves may be due to the fact that earlier electrocardiography (ECG) tracings (when the patient was stable), might have flat or inverted T-waves.
- A rise in serum K^+ above 6 mEq/L often results in a widening of the QRS complex. Unlike a bundle branch block, all parts of the QRS complex are equally affected.
- A rise of serum K^+ above 7 mEq/L is usually associated with a widened P-wave and delayed atrioventricular (AV) conduction. Occasionally, this is accompanied by an elevation of the RS-T junction and a coving of the RS-T segment resembling changes seen in myocardial infarction. This is promptly corrected when the hyperkalemia is treated by dialysis.
- When the serum K^+ is between 7.5 mEq/L and 8 mEq/L, the P-wave disappears, pointing to cessation of atrial contraction. A junctional, and later an idioventricular rhythm is observed. The QRS complex terminally resembles wide sine waves. Death occurs from ventricular fibrillation or cardiac arrest.

Diagnosis

Diagnosis depends on clinical suspicion and the recognition of clinical and ECG features of hyperkalemia. It is confirmed by a rise in serum K^+. A false or pseudohyperkalemia may be observed if blood is hemolysed after collection. Excessive leukocytosis (above 750,000/mm^3) and thrombocytosis (above 1 million/mm^3) can also produce a hyperkalemia due to K^+ release from clotted blood. An unclotted blood sample will give the true serum K^+ value. As with all laboratory investigations, a rise in serum K^+ should be correlated with the clinical picture; when in doubt, it is best to repeat the test.

Management[12-14]

Hyperkalemia should be treated on an emergency footing; it is even more dangerous than hypokalemia. Therapy is always indicated when serum K^+ is above 6 mEq/L, even in the absence of ECG changes, as death can occur in these patients. The following methods are used to reduce the serum K^+ levels—

- *Intravenous calcium gluconate* is the emergency drug of choice when serum K^+ levels are above 7 mEq/L, or if there is evidence of wide QRS complexes, AV block or absent P-waves on an ECG. Between 10–20 mL of 10% calcium gluconate is given as a bolus over 3–5 minutes, and can be repeated after 5–10 minutes, if the ECG remains unchanged after the first injection. Calcium directly antagonizes the effect of K^+ by increasing the membrane threshold, improving conduction, and increasing the force of myocardial contraction. Its effect is temporary and lasts for about 30 minutes. Other measures, therefore, need to be taken after this emergency treatment has been given. Intravenous calcium can produce cardiotoxicity in patients on digitalis—if administered to fully digitalized patients, it is diluted in 100 mL N saline, and given over 30 minutes. Patients with severe hypotension, and those showing an idioventricular rhythm with very wide QRS complexes, may fail to respond to IV calcium. Emergency transvenous pacing should then be tried; this may help to buy time for drugs to act.

- *An insulin-dextrose infusion* will cause a quick shift of K^+ from the vascular and interstitial tissue compartments into the cells. 500 mL of 20% dextrose to which is added 20 units of actrapid insulin is given as an infusion over 1 hour. Hypoglycemia should be watched out for, and if present should be corrected by supplemental glucose. An insulin-glucose infusion can be expected to reduce serum K^+ by 1–2 mEq, and can be repeated after a few hours.
- *An IV infusion of sodium bicarbonate* (50–75 mL of a 7.5% solution), given over 10 minutes. Bicarbonate acts by *shifting K^+ from the extracellular to the cellular compartment*. It is a useful drug, though it may not always be very effective. Repeated use of IV bicarbonate can however aggravate intracellular acidosis and lactic acid production. Intracellular acidosis can result from increased CO_2 production following the use of IV bicarbonate. The CO_2 diffuses into the cells and combines with H_2O to form H_2CO_3. A significant increase in H_2CO_3 within the cells may be incompletely buffered, resulting in intracellular acidosis. Bicarbonate can also bind calcium, so if calcium gluconate has already been used, IV bicarbonate should be given at least 30–60 minutes later. Though some workers hesitate to use bicarbonate because of its possible side effects, we routinely use it to treat hyperkalemia, with satisfactory results.
- *Intravenous furosemide* in a dose of 40–100 mg should be used to promote excretion of K^+ via the urine. This method of course is of no use in patients with renal failure.
- *The use of sodium polystyrene sulfonate resin (Kayexalate)* can cause potassium to be excreted in large quantities via the gut. Polystyrene sulfonate is a cation exchange resin which binds K^+. However, for each mEq of K^+ removed, 2–3 mEq of Na^+ are retained. A sodium overload can therefore occur with frequent use, particularly in the presence of cardiac or renal insufficiency. It can be given orally or as a retention enema. The oral dose of kayexalate is 30 g in 50 mL of 20% sorbitol. The rectal dose is 50 g in 200 mL as a retention enema.
- *Dialysis* is the most effective method of reducing serum K^+ when other methods fail, particularly so in the presence of renal failure. Hemodialysis is preferred as it is quicker; however, peritoneal dialysis though slower, can also serve the same purpose.

HYPOKALEMIA[15]

The serum potassium is normally maintained between 4 mEq/L and 5 mEq/L. A fall in serum K^+ to below 3.5 mEq/L is termed hypokalemia. A serum K^+ level below 2.5 mEq/L is fraught with danger to life. It is being increasingly realized that severe hypokalemia is an important cause of death in critically ill individuals. This danger often goes unrecognized with disastrous consequences.

It has already been emphasized that the major quantity of K^+ within the body is in the intracellular compartment. The total quantity of K^+ in the body is roughly 50 mEq/kg body weight—i.e. 3,500 mEq in a 70 kg adult. Of this, less than 2% (i.e. <70 mEq) is within the extracellular compartment.[14] The large gradient of K^+ between the intracllular and extracellular compartments is due to the activity of the sodium-potassium membrane pump, which actively keeps the potassium within the cellular compartment. Transfer of K^+ from the intracellular to the extracellular compartment (including the vascular compartment) and vice versa, occurs frequently in various disease processes. The reasons or mechanisms underlying these shifts are not always clearly understood. It is obvious therefore, that the serum K^+ does not necessarily reflect changes in total body K^+. In fact, the latter may well be significantly depleted with a normal serum K^+. This is evident if the patient has lost water and K^+ in the same concentration as in plasma. Even if the loss of K^+ exceeds that of water, serum K^+ may be normal in spite of significant body deficit because of shift of K^+ from the cells to the extracellular compartment. Similarly, a raised serum K^+ may occasionally exist with normal or even depleted body stores of K^+. This is illustrated in diabetic ketoacidosis where the serum K^+ can be high even though the total body K^+ is depleted. When diabetic acidosis is corrected, potassium from the plasma and the extracellular compartment moves into the cells, and the body deficit of potassium is now correctly represented by a low serum K^+ concentration.

However, a low serum K^+ invariably indicates depletion of K^+ in the body—in fact, a decrease in serum K^+ is a late finding in K^+ depletion. Thus even a slight decrease in serum K^+ is of import and needs to be corrected.

The etiology of hypokalemia in an ICU setting is due to either loss of K^+ from the body, or a poor intake of K^+, so that a state of negative balance exists, or is due to shifts of K^+ from the extracellular and vascular compartments into the cells.

Loss of K^+

This is generally due to vomiting, diarrhea, nasogastric suction, pancreatic or intestinal fistulae, intestinal obstruction and burns.

Loss of K^+ can also occur through the urine—the most common cause being diuretic therapy in which adequate K^+ replacement has not been taken care of. The urinary K^+ loss in these patients is in excess of 30 mEq/L. Another important cause of increased urinary loss of K^+ with resulting hypokalemia, is the use of corticosteroids; the larger the dose used, the greater the K^+ loss.

Transcellular Shifts

The most important cause of hypokalemia due to shifts of K^+ from the extracellular compartment into the cells is metabolic alkalosis. In this condition, homeostasis induces shift of the H^+ ion from the cells to the plasma to restore pH to normalcy; in exchange, K^+ shifts from the vascular and interstitial tissue compartments into the cells. Beta-2 agonists when given systemically in severe asthma, particularly when combined

with theophylline, can induce a modest fall in serum K^+ through transcellular shifts of K^+.

Diagnosis

The clinical diagnosis rests on the following factors—

- A high index of suspicion of hypokalemia in any critically ill individual where the clinical background suggests a potassium deficit.
- Recognition of clinical features of hypokalemia. At times these are obvious and easily discernible, but unfortunately sometimes they are difficult to detect particularly in critically ill or in obtunded patients.
- Electrocardiographic features suggestive of hypokalemia. In the final analysis hypokalemia can be confirmed only by the estimation of serum K^+ by a flame photometer. It would be a truism to state that every critically ill individual under intensive care will need a serum K^+ estimation to determine the presence or otherwise of changes in this electrolyte.

Hypokalemia produces a disturbance in neuromuscular, muscular, and cardiac function. At times, only cardiac dysfunction is observed; at other times the clinical features are dominated by neuromuscular or muscular dysfunction. Occasionally, both neuromuscular and cardiac dysfunction may be observed. Long-standing K^+ deficits with hypokalemia can also produce a nephropathy characterized chiefly by inability to concentrate the urine. This feature, however, is hardly ever observed in patients under critical care.

Cardiac Dysfunction

This is the most dreaded feature of severe hypokalemia. The most important effect of hypokalemia on the heart is the propensity to cardiac arrhythmias. The most common and earliest abnormalities are ventricular ectopic beats. In ill individuals, the occurrence of such ectopics against a background of a possible potassium deficit should always lead one to suspect hypokalemia. The premature ventricular ectopics may lead to paroxysmal ventricular tachycardia, ventricular fibrillation and sudden death. Paroxysmal ventricular tachycardia may also occur without warning ectopics. In fact, sudden death due to ventricular fibrillation may be the sole catastrophic manifestation of a hypokalemic state.

Many arrhythmias observed during digitalis administration are triggered or worsened by hypokalemia resulting from the associated use of diuretics. Paroxysmal atrial tachycardia, with block and interference dissociation, are two important rhythm disturbances most frequently observed under the above circumstances. The occurrence of these arrhythmias in a patient on digitalis and diuretics should promptly point to underlying hypokalemia.

Marked hypokalemia can also induce hypotension, which is due to a lowered cardiac output and perhaps to poor sympathetic tone related to poor functioning of sympathetic nerve endings.

Neuromuscular and Muscular Dysfunction

Asthenia and apathy are often the earliest symptoms. Whenever the degree of asthenia is more than what is expected in a particular illness, the possibility of hypokalemia should be entertained. The tendon reflexes are sluggish and may be totally absent. Muscle weakness may progress to flaccid paralysis. In severe hypokalemia, the muscles of respiration are involved so that the patient hypoventilates; rarely, the muscles of deglutition may also be affected.

Abdominal distension due to mild ileus and urinary retention are at times the sole presenting features of hypokalemia. In severe cases, a complete paralytic ileus with fluid levels seen on an abdominal X-ray results, closely mimicking an acute abdomen. Following major surgery, hypokalemia is an important cause of delay in return of peristalsis.

Electrocardiography Features

ECG changes may be occasionally observed even with a normal serum K^+ when total body K^+ is markedly depleted. ECG changes frequently (but not necessarily always) appear when the serum K^+ is below 2.5 mEq/L. The following ECG changes may be observed: (1) flattening of T-waves with ST depression of more than 0.5 mm; (2) prominent U-waves, frequently best observed in the precordial leads; (3) occurrence of various arrhythmias as noted earlier.

It is important to realize that ECG changes are nonspecific and unreliable—their absence in no way negates the suspicion of hypokalemia aroused on clinical grounds.

Management[12]

This consists in replacement of K^+ to restore serum potassium levels within the normal range. Whenever possible, it is best to give KCl orally, 1 g thrice daily. Some patients vomit with oral medication, and an important, dangerous side effect following the use of oral potassium tablets, is the occurrence of acute duodenal ulceration with hemorrahge and perforation.

If the serum K^+ is below 3 mEq/L, and certainly if below 2.5 mEq/L, the IV route of administering potassium is to be preferred. Attempts have been made to formulate the K^+ deficit depending on the levels of serum K^+ in plasma. The estimated potassium deficit for a 70 kg adult vis-à-vis the serum K^+ levels is as follows: for aqueous solution. K^+ of 3.0 mEq/dL, the K^+ deficit is 350 mEq constituting about 10% of total K^+; for aqueous solution. K^+ of 2.5 mEq/dL, the K^+ deficit is 470 mEq or about 15% of the total K^+; for aqueous solution. K^+ of 2.0 mEq/dL, the K^+ deficit is 700 mEq or about 20% of the body K^+. These estimates are based on total body potassium of 50 mEq/kg lean body weight, but to my mind, can never even be reasonably accurate. The purpose of the exercise is to stress in general, the magnitude and importance of the problem, and to emphasize the urgency in restoring K^+ deficit.

Ordinarily with a K^+ level of 2.5 mEq/L or less, or if muscle weakness, arrhythmias, or cardiac dysfunction are present, 80–120 mEq of KCl in a dextrose infusion is given

over 24 hours. Replacement is of course adjusted by frequent monitoring of serum K^+ levels. We find this method to be safe and effective. Occasionally, large quantities need to be given at more rapid rates to restore low K^+ levels in the presence of ongoing potassium loss.

The recommended dose for a quicker restoration of serum K^+ levels is 0.7 mEq/kg lean body weight of KCl in a dextrose infusion given over 2 hours. This dose should not increase the K^+ by more than 1–1.5 mEq/L, unless there is metabolic acidosis or renal impairment.

When hypokalemia is below 2 mEq/L, or in the presence of multiple ventricular ectopics or ventricular tachycardia, 60–80 mEq of KCl in a dextrose infusion can be given over 2 hours under carefully monitored conditions.

Certain important features should be kept in mind regarding the IV administration of KCl—

- Intravenous potassium should not be administered, or administered very slowly and with great care, in patients with renal insufficiency or metabolic acidosis.
- Intravenous potassium should not be given through a central vein in high concentrations or at a rate exceeding 40 mEq in 2 hours, as it can result in dangerous, life-threatening cardiac toxicity. When infusing high doses, the use of two separate peripheral veins minimizes the risk of thrombophlebitis, and reduces the pain experienced due to chemical irritation of the venous wall.
- Magnesium depletion promotes potassium loss in the urine and impairs movement of K^+ from the cellular into the vascular compartment. The reason for this is not clear. From the practical point of view, if serum K^+ levels are difficult to raise, then the possibility of magnesium depletion should be entertained, and the magnesium deficit should be corrected. This generally allows for a quick restoration of serum K^+ levels to the normal range.

CALCIUM AND PHOSPHORUS[12,16-19]

The description of disturbances in calcium and phosphorus balance given below is chiefly with reference to critically ill patients under intensive care. Almost always, changes in serum calcium or phosphorus in an ICU setting, serve as markers of the severity of the illness, and do not in themselves pose major clinical problems nor do they present difficulties in management.

The normal total serum calcium is 8.5–10.2 mg/dL. About 50% of this calcium is bound to serum proteins, chiefly to albumin. An additional 5–10% is in combination with anions like bicarbonate, and the remaining is in the free or ionized form. The ionized form is the physiologically active component of calcium, and measures 4.8–7 mg/dL. It is to be noted that laboratory tests indicate the total serum calcium levels, and not the active ionized calcium level. The total serum calcium level does not always reflect the level of ionized calcium. Thus, a decrease in serum proteins, and in particular of serum albumin, leads to a decrease in the protein-bound fraction and in the total calcium, even though the ionized calcium remains unchanged. A hypocalcemia may be wrongly diagnosed under these circumstances. In hypoalbuminemic states, a correction factor that increases the total calcium by 0.75 mg/dL for each 1 g/dL decrease in serum albumin below 3.5 g/dL, gives a more correct picture of serum calcium levels. Ion-specific electrodes can however directly measure ionic calcium, allowing a very accurate quantification of the physiologically active calcium in the serum. Unfortunately, only few reference laboratories can measure ionic calcium levels in the blood.

In an ICU setting, the most common causes of lowered serum calcium levels are related to hypoalbuminemia. If these are excluded, then low serum calcium levels (i.e. low-ionized calcium levels) are invariably related to the causes listed below.

Alkalosis

An increase in the pH promotes binding of calcium to albumin (even though albumin levels are unchanged), and reduces ionic serum calcium; the total serum calcium however remains unchanged. Both metabolic and respiratory alkalosis can produce a fall in ionic serum calcium.

Sepsis

Hypocalcemia is observed at times in sepsis. This could be due to a respiratory alkalosis produced by increased ventilation commonly observed in these patients, as also due to efflux of calcium across a disrupted, damaged microcirculation.

Hypomagnesemia

Depletion of magnesium inhibits parathormone secretion and reduces the response of the end organ to parathormone, resulting in hypocalcemia. Hypocalcemia due to magnesium depletion is difficult to correct, as the infused calcium is excreted via the urine due to diminished action of the parathyroid hormone. Once the magnesium deficiency is corrected, serum calcium is quickly restored to normal. In the presence of normal renal function and in the absence of hypoalbuminemia, sepsis or alkalosis, a persistently low serum calcium in an ICU setting should always suggest the strong possibility of an associated magnesium deficiency. The combined presence of hypokalemia in the above situation strengthens the diagnosis of hypomagnesemia even if the serum Mg^{++} levels are normal.

Renal Failure

The serum calcium in renal failure may be normal, low or increased depending on the nature of metabolic abnormality induced in a given patient.

Pancreatitis

A low serum calcium is invariably present in severe pancreatitis, and it serves as a marker for the severity and prognosis of the disease.

Box 3: Common causes of hypocalcemia in an ICU setting

- Related to hypoalbuminemia (the most common cause)
- Metabolic or respiratory alkalosis
- Sepsis
- Hypomagnesemia
- Renal failure
- Pancreatitis
- *Other causes:* burns, massive blood transfusions, following cardiopulmonary bypass, and in fat embolism

Other causes of hypocalcemia in an ICU setting include burns, massive blood transfusions, following cardiopulmonary bypass and in fat embolism. In massive blood transfusions, the citrate preservative in banked blood binds calcium, whilst in fat embolism the circulating free fatty acids bind calcium causing hypocalcemia.

The common causes of hypocalcemia are given in Box 3.

Clinical Features

Hypocalcemia can cause tetany (carpopedal spasm), and neuromuscular excitability, which in severe cases can manifest with seizures.

Hypotension, vasodilatation, and a prolonged QT interval are also observed in severe hypocalcemia.

In an ICU setting, clinical features resulting from hypocalcemia are rarely observed. The hypocalcemia in critically ill patients as already mentioned, often draws attention to the nature and severity of the underlying illness, and at times is of prognostic value.

Management

Mild asymptomatic hypocalcemia requires no specific treatment. Well-marked hypocalcemia and symptomatic hypocalcemia are treated with IV calcium gluconate, 10 mL being given very slowly over 10 minutes and repeated if necessary. A maintenance drip of 10 mL calcium gluconate in 100–200 mL 5% dextrose saline given over 2–3 hours can then be administered.

HYPERCALCEMIA

Hypercalcemia is a dangerous metabolic disturbance; serum calcium levels above 14 mg percent can cause death if not promptly recognized and treated. There are many causes of hypercalcemia, the important ones are listed in Box 4.

Box 4: Important causes of hypercalcemia

- Primary hyperparathyroidism
- Metastatic carcinoma
- Sarcoidosis
- Myelomatosis
- Vitamin D intoxication
- Milk-alkali syndrome
- Ectopic parathyroid hormone producing tumors
- Hyperthyroidism
- Adrenal insufficiency
- Dysproteinemia
- Myxedema
- Osteoporosis following prolonged immobilization

The two most frequent causes in the ICU are hypercalcemia due to hyperparathyroidism, and that secondary to malignant disease.

The clinical features of hypercalcemia are varied, often misleading the physician with a wrong diagnosis. Drowsiness and mental apathy may simulate a stroke. Changes in mental state may lead to a wrong diagnosis of depression. Ileus, urinary retention, excessive muscular weakness and increasing renal failure are some of the other manifestations of an underlying hypercalcemia.

Management[17-19]

Hypercalcemia above 13 mg/dL or hypercalcemia associated with symptoms needs prompt treatment.

Volume Load Plus Furosemide

Hypercalcemia leads to increased excretion of calcium in the urine, with a resulting osmotic diuresis. Hypovolemia with marked hemoconcentration of the blood results. Multiple infusions of normal saline to increase the circulating volume produce a natriuresis, which in itself promotes excretion of calcium, and results in lowering of serum calcium levels.[17,18] It is preferable to combine a volume load (N saline infusion) with IV furosemide 40–60 mg given every 2–4 hours. The volume lost in the urine should be promptly replaced with N saline so that the "intake" matches the "output". The strategy is to aim at a larger output of urine, and yet replace it with an equivalent large "input" of N saline. Potassium replacements will also be necessary as diuresis progresses. Care must be taken to ensure that elderly patients or those with poor left ventricular function are not overhydrated and pushed into pulmonary edema.

Calcitonin

This drug can reduce serum calcium by inhibiting bone resorption. Salmon calcitonin is rapid acting, but expensive; it can effectively reduce the serum calcium within 2–3 hours.[19] It is administered subcutaneously or intramuscularly in a dose of 4 mg/kg every 12 hours for two doses. The dose can be doubled if the desired effect on serum calcium is not obtained within 2 days.

Mithramycin

This is an antimitotic drug, which reduces serum calcium by inhibiting bone resorption. It is slower acting (24–36 hours

Box 5: Common causes of hypophosphatemia

- Dextrose infusions
- Nutritional recovery syndrome
- Use of aluminum hydroxide as antacid
- Sepsis
- Diabetic ketoacidosis
- Respiratory alkalosis

to act) than calcitonin; the latter is therefore preferred for emergency use. It is given in a dose of 25 μg/kg preferably, in an infusion over 6 hours, and can be repeated after 2–3 days.[19] The risk of bone marrow depression is small as the dose used is less than that used in neoplastic diseases.

Calcitonin and mithramycin are often unavailable in developing countries.

Dialysis

Hemodialysis in particular, can effectively and quickly reduce serum calcium levels. It should be tried if other methods are ineffective. If saline diuresis is not possible as in patients with renal failure, hemodialysis is the only effective therapy for severe hypercalcemia.

PHOSPHORUS[20,21]

The normal serum phosphate level is between 3 mg/dL and 4.5 mg/dL. There is a slight diurnal variation in serum phosphate levels, the latter being lower in the mornings and higher at night. Phosphorus is chiefly an intracellular ion and less than 1% is located in the extracellular fluid compartment.

Hypophosphatemia is uncommonly met with in patients under critical care, or for that matter even in patients admitted to the general wards of a hospital.

The important causes of severe hypophosphatemia in a hospital population are given in Box 5.

Dextrose Infusions

This is probably the most important cause of hypophosphatemia. Phosphate levels were observed to fall within a few hours of IV dextrose infusions, particularly in alcoholics and debilitated patients. Increasingly low phosphate levels were also observed by the 10th day of starting total parenteral nutrition. Hypophosphatemia associated with dextrose infusions is related to transport of glucose and phosphorus into the liver and skeletal muscle through insulin action. The phosphorus within the cells is used as a co-factor for glycolysis. In adequately nourished patients infusions of IV dextrose do not affect phosphate levels, but in malnourished individuals, a sharp fall in the phosphate levels to less than 0.5 mg/dL may occur within a few days.

Nutritional Recovery Syndrome

Overzealous feeding, in particular, with a high carbohydrate intake in malnourished patients results in an illness characterized by lethargy, weakness, diarrhea and multiple electrolyte abnormalities which include a low phosphate level. Death can also result. This is the reason why feeds should be gradually increased in malnourished or very ill individuals.

Use of Aluminum Hydroxide as an Antacid

Aluminium hydroxide when used as an antacid binds phosphate in the bowel and produces phosphate depletion. Aludrox and digene are the two most common antacids used in India, and unfortunately most critically ill patients seem to be receiving these drugs.

Sepsis

Hypophosphatemia has been reported in sepsis, and can occur early in the natural history of sepsis. The mechanism leading to hypophosphatemia in sepsis is however unknown.

Diabetic Ketoacidosis

Glycosuria in diabetic ketoacidosis produces a loss of phosphate in the urine leading to depletion in the phosphorus content of the body. The serum phosphate level however may be normal because of the transfer of phosphates from the intracellular compartment to the extracellular one. During therapy with insulin the phosphate from the vascular and interstitial tissue compartment returns into the cells and a marked fall in plasma phosphate levels is observed. Nevertheless, specific replacement of phosphorus does not seem to improve the outcome of diabetic ketoacidosis.

Respiratory Alkalosis

This is an important cause of hypophosphatemia. The increase of pH within the cells promotes glycolysis and this induces the influx of phosphorus into the cellular compartment. Hypophosphatemia can thus occur in patients who are being overventilated whilst on ventilator support.

Clinical Features[20,21]

Even well-marked hypophosphatemia is often silent. Low phosphate levels are associated with depleted stores of 2,3-diphosphoglycerate within the red blood cells, causing a leftward shift of the oxyhemoglobin dissociation curve. As a consequence, oxygen bound to hemoglobin is less easily released to tissues.

Very low phosphate levels have been rarely reported to cause hemolysis.[20] Hypophosphatemia reduces cardiac contractility and when severe and chronic, has been reported to cause cardiomyopathy.[20]

The only convincing clinical feature of hypophosphatemia is the occurrence of proximal muscle weakness resembling a myopathy. We observed it in a patient who was taking excessive doses of aluminum hydroxide. The muscle weakness was associated with very low phosphate levels. Complete recovery ensued on stopping the antacid and on increasing the oral phosphate intake.

Management[12,21]

Phosphate levels below 1 mg/dL require IV replacement even when no obvious clinical disorder is evident. The recommended solution for use contains sodium phosphate (3 mM phosphorus/mL), potassium phosphate (3 mM phosphorus/mL), and neutral sodium phosphate (0.09 mM phosphorus/mL). When the serum phosphate level is below 0.5 mg/dL, the dose recommended is 0.5 mM/kg over 4 hours. When the serum phosphate level is between 0.5 mg/dL and 1 mg/dL, the dose recommended is 0.2 mM/kg over 4 hours.[21] Rapid infusion has been known to produce hypotension.[21] Hypophosphatemia is often associated with hypokalemia, hypocalcemia and hypomagnesemia. These electrolytes should be monitored, and if necessary, also replaced.

HYPERPHOSPHATEMIA[12]

Hyperphosphatemia is chiefly observed in renal failure when the glomerular filtration rate drops below 25 mL/minute. Widespread cellular necrosis as in patients with tumor lysis or rhabdomyolysis is also associated with hyperphosphatemia due to release of phosphate from damaged or destroyed cells. Diabetic ketoacidosis may be associated with a rise in serum phosphate even though body phosphates are depleted.

Management

Management of hyperphosphatemia is directed toward the underlying cause. Aluminum hydroxide orally is often used in chronic renal failure to bind phosphates within the gut and thereby reduce the degree of hyperphosphatemia.

MAGNESIUM ION

Increasing attention has been given to this ion in the last 10 years. Magnesium (Mg^{++}) has a significant presence (second only to K^+) as an intracellular cation. It is an essential co-factor in enzymatic reactions involving adenosine triphosphate, and as part of the membrane pump it helps to maintain electrical excitability in nerves and muscles. The recommended daily intake of magnesium is 6–10 mg/kg per day and the normal serum magnesium concentration is 1.5–2 mEq/L.

How important is the ion in critical care medicine? The difficulty in answering this query in critically ill patients stems from the fact that the magnesium ion is not uniformly distributed in body fluids. Only 0.3% of the body magnesium is in the serum and as much as 50% is within the bones. The magnesium distribution in adults is shown in Table 1. Hence, changes (in particular deficiencies) in body magnesium are unlikely to be reflected in the serum Mg^{++} levels, which can be normal in both Mg^{++} deficiency or excess. How then does one authenticate clinical features attributable to magnesium deficiency? And how does one gauge the true prevalence of Mg^{++} insufficiency in critically ill patients? There are a number of specialists in critical care medicine who feel that magnesium depletion is very frequent in an ICU population chiefly due to the lack of daily supplements, and the frequent use of diuretics in these patients.

Table 1: Magnesium distribution in adults[22]

Tissue	*Content (nmoles)*	*Total Body Mg (%)*
Serum	2.6	0.3
RBCs	5.0	0.5
Soft tissue	193	19.3
Muscle	270	27.0
Bone	530	53.0

Abbreviation: RBCs, red blood cells.

The important causes of Mg^{++} deficiency include[23]—

- Diuretics, in particular furosemide, which blocks reabsorption of Mg^{++} through the loop of Henle, causing an increased excretion of Mg^{++} in the urine.
- Alcoholism, which induces magnesium depletion chiefly through increased excretion of the ion in the urine. Magnesium deficiency may become manifest soon after ethanol withdrawal.
- Diarrhea, which causes loss of the ion, as secretions within the lower GI tract are rich in Mg^{++}.
- Aminoglycosides, which act by reducing reabsorption of Mg^{++} in the renal tubules.
- Reduced intake in critically ill individuals in the presence of abnormal losses of this ion.

Clinical Features[23]

The clinical diagnosis of Mg^{++} deficiency leaves much to be desired. Colleagues interested in this field diagnose Mg^{++} deficiency even with normal levels of serum Mg^{++}. The clinical situations suggestive of Mg^{++} deficiency include—

- Presence of other electrolyte abnormalities—in particular hypokalemia, hyponatremia, hypocalcemia and hypophosphatemia. Of all these, the association between hypokalemia and hypomagnesemia is now fairly well established. Refractory hypokalemia, at least in some patients, may be due to an associated hypomagnesemia. Repletion of Mg^{++} in such patients leads to a rapid correction of the K^+ deficit.
- Intractable arrhythmias have been dubiously ascribed to Mg^{++} deficiency. It is true that IV magnesium is occasionally an effective antiarrhythmic agent when other antiarrhythmic drugs have failed. But this could well be related to the specific antiarrhythmic effect of the ion, rather than to a true deficiency.
- Arrhythmias in myocardial infarction—magnesium infusions have been reported to reduce the incidence of arrhythmias in acute myocardial infarction and hypomagnesemia can enhance calcium entry into vascular smooth muscle of the coronaries, and initiate vascular spasm. The role of hypomagnesemia in relation to the clinical aspect described above.

- Muscle weakness has been occasionally reported with hypomagnesemia, but here again the evidence is unconvincing. Neuromuscular excitability with a positive Chvostek's or Trousseau's sign has also been reported. Seizures have also been noted to be a feature of severe hypomagnesemia.

In our opinion, the clinical features of import with reference to hypomagnesemia, are the presence of hypokalemia and cardiac arrhythmias in a setting where Mg^{++} loss through the urine or the gut, is likely to be increased.

Magnesium Replacement[24]

In patients with symptomatic Mg^{++} depletion and normal renal function, magnesium sulfate is given at the rate of 1 mEq/kg for the first 24 hours, and then at 0.5 mEq/kg for the next 3 days. Magnesium sulfate is available as a 10% or a 50% solution. 5 mL of the 10% or 1 mL of the 50% solution will provide 4 mEq of elemental magnesium. The 50% solution must be diluted before use.

In the presence of life-threatening hypomagnesemia causing cardiac arrhythmias or seizures, 4 mL of a 50% solution of magnesium sulfate is infused over 2 minutes. This is followed by 10 mL of 50% magnesium sulfate in 500 mL of N saline over the next 6 hours. 12 hourly infusions of 10 mL of 50% magnesium sulfate are then recommended for the next 5 days.

Magnesium administration should always be monitored by serum magnesium levels. Great care needs to be taken in administering magnesium intravenously in patients with renal insufficiency. The dose stated above is preferably halved, and given over double the time.

HYPERMAGNESEMIA[25]

Hypermagnesemia generally occurs in patients with chronic renal failure who are administered magnesium-containing antacids orally over prolonged periods of time. Diabetic ketoacidosis complicating renal failure induces magnesium transport from the intracellular to the extracellular compartment, and can raise serum Mg^{++} levels.

The most important clinical feature of hypermagnesemia is hypotension which is observed when Mg^{++} levels exceed 3–5 mEq/L. The hypotension does not respond to the usual measures. Complete heart block is observed with serum Mg^{++} levels of 7.5 mEq/L; respiratory depression and mental obtundation progressing to coma, occur with serum Mg^{++} levels of 10 mEq/L.

Treatment

Magnesium levels can be lowered and magnesium induced hypotension best countered by administering 20 mL of 10% calcium gluconate intravenously. Magnesium excretion in the urine can be induced by the use of IV furosemide. If renal function permits, a volume load should precede the use of furosemide. Hemodialysis can effectively lower elevated serum magnesium levels, and is the treatment of choice in patients with severe renal failure.

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SECTION

11

Acid-Base Disturbances in the Critically Ill

- Acid-Base Disturbances in the Critically Ill

CHAPTER 41

Acid-Base Disturbances in the Critically Ill

GENERAL CONSIDERATIONS

The maintenance of normal acid-base balance (pH 7.35–7.45) in the blood is of crucial importance and is a vital homeostatic function of the body. Any variation from the normal constitutes an emergency in that a significant change in the hydrogen ion (H^+) concentration of the plasma or the extracellular fluid is incompatible with life; a pH less than or equal to 7, or a pH more than or equal to 7.8 spells imminent danger and death.

Acid-base disturbances occur very frequently in patients who are critically ill. They may dominate the clinical picture as in severe diabetic ketoacidosis or in renal failure. The diagnosis and importance of acid base changes in these patients is obvious and is quickly appreciated. However, more often than not a change in the acid-base equilibrium occurs surreptitiously against the background of a critical illness. The manifestations of an altered acid-base homeostasis in such patients are often subtle, virtually impossible to clinically detect, and are often masked by the clinical features of the illness. There are no barriers to these disturbances; they are encountered in all fields and all specialties of medicine and surgery. Not uncommonly, the realization that sudden clinical deterioration or death in a particular patient may have been related to acid-base disturbances dawns on the physician a trifle too late. An early diagnosis of a change in acid-base equilibrium demands a sharp clinical acumen, a grasp of the physiopathology underlying these changes, and an intelligent interpretation of laboratory data.

No satisfactory assessment of the presence and degree of acid-base disturbances can be made without measuring the pH of the blood by the pH electrode. It is imperative that the importance of pH and acid-base measurements through a blood gas machine using the Astrup technique is universally recognized in all developing countries. Today, although many critical care units in the large metropolitan cities of India provide this very necessary facility, a number of critical care units in smaller cities still lack this basic amenity. Most students and doctors are taught to interpret arterial blood gases and acid-base disturbances by rule of the thumb or by reference to standard charts and graphs, which allow a prompt solution for the basic problem. This may be satisfactory—but only to a point. Correct interpretation of blood gases and acid-base disturbances necessitates a familiarity with basic physiology in this field. Then only can altered physiology in a critically ill individual be better understood. Intelligent and in-depth interpretation leads to a more rational management of the patient as a whole.

This chapter first outlines the elementary basics necessary for satisfactory clinical interpretation. It then deals with the clinical description, the laboratory interpretation and assessment, and the treatment of these disturbances.

BASIC CONCEPTS

Concept of an Acid

An acid is a potential H^+ or proton donor. Conversely a base is a potential proton acceptor.

The strength of an acid (HA) is measured by the extent to which it dissociates in an aqueous solution.

$$HA \rightleftharpoons [H^+] + [A^-]$$

When the above reaction is in equilibrium, for a strong acid $[H^+] + [A^-]$ will be in a greater concentration than HA in the undissociated form. Also, at equilibrium, the product of the

Table 1: Correlation between H^+ concentration and pH values

Hydrogen ion concentration (nmoL/L)	*pH*
10	8.00
20	7.70
30	7.52
40	7.40
50	7.30
60	7.22
70	7.15
80	7.10
90	7.05
100	7.00

concentration on one side of the equation will bear a constant relationship to the product of concentration on the other.

$$Ka\,[HA] = [H^+]\,[A^-]$$

$$Ka = \frac{[H^+]\,[A^-]}{[HA]}$$

where Ka is the acid dissociation constant. Strong acids have a high Ka. Similar equations would apply to the dissociation of a base.

Concept of pH

The acidity of an aqueous solution is measured by its H^+ concentration or activity. The H^+ activity is expressed as pH. This terminology was introduced to simplify expression of a wide range of H^+ found in various fluids within the body. A quantification of H^+ in various fluids in moles, would have been cumbersome and difficult. The notation pH is the negative logarithm of H^+ concentration. This allows a large range of H^+ concentrations to be simply expressed and measured. Thus,

$$pH = \log \frac{1}{[H^+]}$$

$$= -\log 10\,[H^+]$$

= negative exponent of an expression of $[H^+]$ to the power 10

Thus, a pH of 7.4 = $[H^+] \times 10^{-7.4}$

The normal H^+ concentration of blood is 40 nmoL/L or 40×10^{-9} moles/L. This is equivalent to a pH of 7.4. Changes in acid-base balance can be looked upon either as changes in the H^+ concentration or changes in pH. Table 1 given below shows the H^+ concentration in relation to the corresponding pH values.

Henderson-Hasselbalch Equation

In the earlier section on the Concept of an Acid, it has been noted that—

$$Ka = \frac{[H^+][A^-]}{[HA]}$$

If we wish to express H^+ concentration as pH (log 1/H), we may rewrite the above equation thus—

$$[H^+] = Ka\,\frac{[HA]}{[A^-]}$$

Taking reciprocals,

$$\frac{1}{[H^+]} = \frac{1}{Ka} \times \frac{[A^-]}{[HA]}$$

Taking logs,

$$\log \frac{1}{[H^+]} = \log \frac{1}{Ka} + \log \frac{[A^-]}{[HA]}$$

$$\text{i.e. } pH = pKa + \log \frac{[A^-]}{[HA]}$$

where pKa is the negative logarithm of the dissociation constant Ka. The above is the Henderson-Hasselbalch equation.

Buffers

Buffers are substances, which react with an acid or base and thereby minimize changes in pH. The metabolic processes within the body add a daily load of H^+ to the body. These H^+ if not properly dealt with within the body would produce a disastrous rise in H^+ concentration, and a catastrophic fall in the pH. The homeostasis of acid-base balance however remains unchanged because of the buffering systems within the body and due to the role of the kidneys.

The main buffer systems of the body are—

- Hemoglobin and to a much lesser extent organic phosphates within the red blood cells.
- Bicarbonates (HCO_3^-) and inorganic phosphates within the blood.
- Plasma proteins.
- Tissue proteins.
- Minerals (phosphates, carbonates) within the bones.

It is only possible in this book to deal with the HCO_3^- carbonic acid buffer systems. The reader is referred to a standard textbook on Physiology for a more thorough understanding of the subject.

The HCO_3^--carbonic acid reaction is important in regulating acid-base balance. It constitutes a weak buffer system, which can be used as a measure or reflection of all acid-base reactions within the body, because buffer systems are in dynamic equilibrium, and carbon dioxide (CO_2) diffuses freely across all tissues and membranes. Also, these chemical reactions occur very rapidly.

The CO_2 produced by tissue metabolism diffuses into plasma and the RBCs. The enzyme carbonic anhydrase within the RBCs catalyzes the formation of carbonic acid—

$$H_2O + CO_2 = H_2CO_3$$

The carbonic acid within the RBCs is dissociated thus—

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

The HCO_3^- within the RBCs diffuses out into the plasma, while the H^+ is mopped up by the hemoglobin, which acts as a buffer base. The loss of one ion from the cell has to be compensated by the entry of an equivalent ion. Thus, chloride ions (Cl^-) from the plasma enter the RBCs in place of the HCO_3^- ions, which have diffused out into the plasma.

When the blood reaches the lungs, the chloride (Cl^-) shift is reversed and HCO_3^- enters the RBCs. The HCO_3^- within the RBCs breaks down into H_2O and CO_2. The CO_2 diffuses out through the capillaries into the alveoli, and is washed out into the outside air.

The HCO_3^--carbonic reaction can be looked at from another angle as regards the role it plays in controlling acid base balance. Thus, when H^+ enters tissue fluids—

$$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons CO_2 + H_2O$$

The CO_2 is rapidly washed out via the lungs leading to a rapid control of H^+ production, but of course at the expense of a fall in HCO_3^-.

The Henderson-Hasselbalch equation for the HCO_3^--carbonic acid reaction aptly illustrates the role played by this reaction in regulating acid-base balance.

$$pH = pK + \log \frac{HCO_3^-}{H_2CO_3}$$

$$pH = 6.1 + \log \frac{HCO_3^-}{H_2CO_3}$$

$$pH = 6.1 + \log \frac{HCO_3^-}{0.03 \times PCO_2}$$

where 0.03 is the solubility of CO_2 in plasma, and PCO_2 the partial pressure of CO_2 in plasma.

If instead of pH one considers the H^+ concentration, then the following modification of the Henderson-Hasselbalch equation can be used.

$$[H^+] = 24 \times \frac{PCO_2}{HCO_3^-} \text{nmoL/L}$$

Normally, $[H^+] = 24 \times 40/24 = 40$ nmoL/L (pH 7.4).

The Henderson-Hasselbalch equation expresses the relationship between three reactants: H^+, HCO_3^- and PCO_2, and can be used as an expression of acid-base balance within the body.

ROLE OF THE KIDNEYS IN ACID-BASE BALANCE

The kidneys play an important and crucial role in H^+ regulation. They do so in the following ways—

- *Regulating excretion and reabsorption of bicarbonate* Bicarbonate is filtered by the glomerulus, the quantity of HCO_3^- in the filtrate being dependent on the plasma bicarbonate, and the glomerular filtration rate. The HCO_3^- is then dealt with as follows—
  - Reabsorption of HCO_3^- in the proximal renal tubules at a rate, which is dependent on the PCO_2. The higher the PCO_2, the greater the degree of HCO_3^- reabsorption; the lower the PCO_2, the lesser the degree of reabsorption of HCO_3^-, and the greater its excretion. This enables respiratory acidosis (due to a high $PaCO_2$) to be compensated through retention of HCO_3^-, and respiratory alkalosis (due to a low $PaCO_2$) to be compensated by an increased excretion of HCO_3^- (see subsections on Respiratory Acidosis and Respiratory Alkalosis).
  - In metabolic acidosis, H^+ is excreted into the urine. The enzyme carbonic anhydrase catalyzes the reaction

    $$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$$

    The CO_2 is reabsorbed and is excreted into the lungs. This is an important means by which the pH is controlled.
- *Use of buffering systems* Hydrogen ions can be mopped up by phosphate buffers, thus tending to increase the pH, while at the same time conserving HCO_3^-.

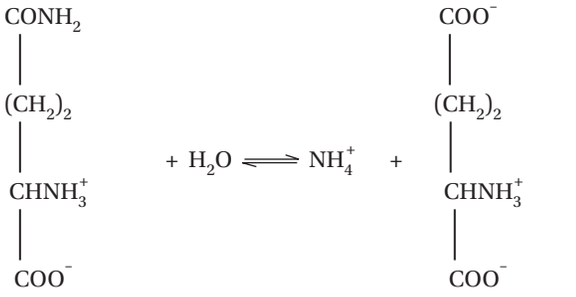
  Thus, under the influence of carbonic anhydrase—

  $$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \text{ (in the tubular cells)}$$
  $$H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

  The HCO_3^- ion is reabsorbed. The H^+ is mopped up by $NaHPO_4$ thus—

  $$H + NaHPO_4 \rightleftharpoons NaH_2PO_4$$

  this is excreted via the urine.
- Formation of ammonia. NH_4^+ is formed in the tubular cells by conversion of glutamine to glutamate. Thus,



GLUTAMINE GLUTAMATE

  NH_4^+ combines with chloride (Cl^-) and is excreted via the urine, the reaction being controlled by the enzyme glutaminase. NH_4^+ excretion to be fully operative takes time. It is however an extremely important mechanism for pH control, as excretion of ammonia allows the excretion of a significantly large quantity of H^+ via the kidney.
- *Reabsorption of sodium* The active reabsorption of sodium (Na) from the filtrate into tubule cells causes a potential gradient across the cell membrane. The positively charged

H^+ within the tubule cell thus passes across the membrane into the filtrate, and is buffered within the filtrate by a phosphate buffer.

$$H + NaHPO_4 \rightleftharpoons NaH_2PO_4$$

- In summary, the kidneys help to maintain acid-base balance in the following ways—
  - Retention of HCO_3^- when the PCO_2 increases.
  - Excretion of HCO_3^- when the PCO_2 falls.
  - Reabsorption of HCO_3^- when there is accumulation of H^+ in the blood.
  - Excretion of titratable acid and NH_4^+ to counter an increase of H^+ in the blood.
  - Excretion of H^+ when there is a primary loss of HCO_3^-.
  - Increased HCO_3^- excretion in the urine, together with a loss of K^+ in the urine, when there is a primary increase in plasma HCO_3^-.

11

DISTURBANCES IN ACID-BASE BALANCE: TERMINOLOGY

Terms used: acidemia, alkalemia, acidosis, alkalosis.

- The normal pH of arterial blood is maintained within the range of 7.35–7.45.
- Acidemia exists when the pH of arterial blood is below the normal range, i.e. less than 7.35.
- Alkalemia is the state in which pH of arterial blood is above the normal range, i.e. greater than 7.45.
- Acidosis is an abnormal state leading to an increase in the acid in the body.
- Alkalosis is an abnormal state leading to a fall in acid or an increase in the alkali in the body.
- When acidosis induces compensatory changes in the body so that pH remains within the normal range, it is termed compensatory acidosis. When acidosis produces a fall in pH below 7.35, it is termed uncompensated acidosis. Uncompensated acidosis and acidemia are thus synonymous.
- Similarly, alkalosis can be compensated or uncompensated, and alkalemia is synonymous with the latter.
- Acidosis and alkalosis (as also acidemia and alkalemia) may result from primary respiratory or metabolic disturbances so that we have respiratory acidosis and metabolic acidosis, as also respiratory alkalosis and metabolic alkalosis.
- Respiratory acidosis and respiratory acidemia (uncompensated respiratory acidosis) result from alveolar hypoventilation, which leads to hypercapnia.
- Respiratory alkalosis and respiratory alkalemia (uncompensated respiratory alkalosis) result from alveolar hyperventilation, which causes hypocapnia.
- Metabolic acidosis and metabolic acidemia are caused by either accumulation of acid or loss of base from the body.
- Metabolic alkalosis and metabolic alkalemia are due to accumulation of base or loss of acid from the body.
- Mixed acid-base disturbances are caused by a combination of respiratory and metabolic factors.

LABORATORY DIAGNOSIS OF ACID-BASE DISTURBANCES

A suspicion of possible acid-base disturbances should always be entertained in each and every patient with a critical illness. Disturbances in acid-base equilibrium can also occur under some reasonably well-defined clinical conditions. Thus in an unconscious hyperpneic patient, the possible diagnosis of diabetes or uremia should be established by relevant blood and urine tests, and in suspected aspirin poisoning, the acetyl salicylic acid levels in the blood confirm the diagnosis. Such investigations help in two ways: (1) they point to the possible nature of the acid-base disturbance and (2) they direct attention to the root cause of such a disturbance, which proves invaluable in the management of the patient.

ESTIMATION OF SERUM ELECTROLYTES

This is mandatory in every patient with acid-base disturbances, as electrolyte abnormalities are frequently seen and are often inseparable from changes in acid-base balance. Thus, hyperkalemia is frequently seen in metabolic acidosis, and hypokalemia and hypochloremia are commonly observed in metabolic alkalosis.

INTERPRETATION OF pH AND ACID-BASE MEASUREMENTS BY THE ASTRUP TECHNIQUE

In this technique, the pH and PCO_2 of the blood are measured by a sensitive instrument (radiometer). The values of standard HCO_3^-, actual HCO_3^-, CO_2 content, and base excess or deficit are then read from a standard nomogram. These concepts are briefly explained below.

The standard HCO_3^- is the HCO_3^- content in the plasma of blood, which has been equilibrated at a PCO_2 of 40 mm Hg, as also with oxygen so as to saturate it with oxygen. The standard HCO_3^- is a measure of the nonrespiratory HCO_3^-. It is the most active, mobile, rapidly reacting fraction of the total buffer potential, and its rate of excretion and retention is governed by the kidneys. A fall in the standard HCO_3^- therefore indicates a metabolic acidosis; conversely a rise in the standard HCO_3^- indicates a metabolic alkalosis. A normal standard HCO_3^- indicates metabolic equilibrium.

The actual HCO_3^- content is the HCO_3^- concentration in mEq or mmoL/L in the plasma. It is not directly estimated; its value is derived from a nomogram in the Astrup technique, or from the CO_2 content of blood, which can be estimated by the van Slyke Apparatus.

The CO_2 content of plasma is the actual HCO_3^- content + dissolved CO_2. As stated above, it can be estimated by gasometry (Van Slyke Apparatus), or is derived from a nomogram if the pH and $PaCO_2$ are known.

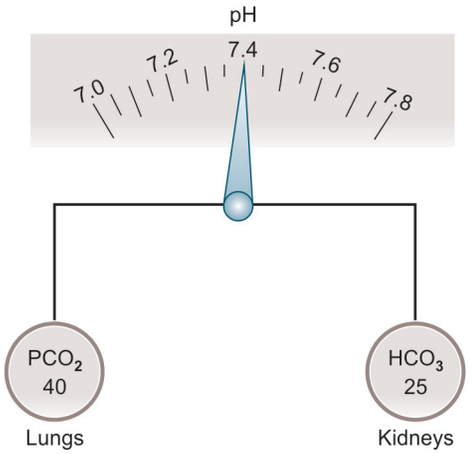


Fig. 1: Normal acid-base balance

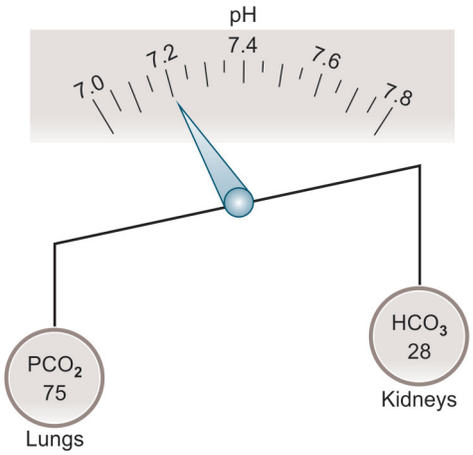


Fig. 2: Uncompensated respiratory acidosis and acidemia

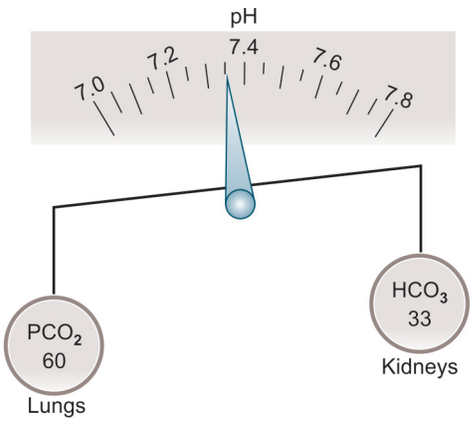


Fig. 3: Compensated respiratory acidosis

Base excess defines the presence in blood of excess or deficit of base, the physiological range being ±2.3 mEq/L. It denotes the amount of strong acid or base per liter of blood, which has been added as a consequence of a metabolic disturbance. It is an in vitro concept, and is again derived from a nomogram if the pH and $PaCO_2$ are known.

Some of the terms described above are apt to prove confusing to the resident working in critical care medicine. For purposes of simplification, acid-base changes are best interpreted by a consideration of the Henderson-Hasselbalch equation—

$$pH = pK + \log \frac{HCO_3^-}{PCO_2 \times 0.03}$$

In other words, pH is the "balance" between the respiratory parameter represented by $PaCO_2$, and the metabolic parameter represented by HCO_3^-. This is most simply illustrated in Figure 1.

A primary change in the respiratory parameter ($PaCO_2$) disturbs the "balance" illustrated in Figure 1 to produce respiratory acid-base disturbances; a primary change in the metabolic parameter (HCO_3^-) disturbs the balance and produces metabolic acid-base disturbances.

A rise in $PaCO_2$ primarily due to alveolar hypoventilation causes respiratory acidosis, and when this acidosis lowers the pH to less than 7.35, respiratory acidemia results. A fall in $PaCO_2$ produced by hyperventilation induces respiratory alkalosis and if the pH rises to more than 7.45, respiratory alkalemia results.

Homeostasis demands that primary changes in $PaCO_2$ lead to secondary changes in the plasma HCO_3^-, so that the pH is kept within the normal range as far as possible. An acute rise in $PaCO_2$ (due to sudden hypoventilation following poisoning or a near respiratory arrest), will lead to a very small rise in the plasma HCO_3^- (described in subsection on HCO_3^--carbonic acid reaction). The degree of retention of plasma HCO_3^- is just 0.1 mmoL or 0.1 mEq per 1 mm Hg rise in $PaCO_2$. The standard HCO_3^- will remain unchanged. This can produce a gross imbalance between the respiratory and metabolic parameters, and can lead to a sharp and dangerous fall in pH (Fig. 2).

On the other hand, a slow or chronic rise in $PaCO_2$ (so frequently observed in patients with chronic airways obstruction) allows renal compensation to come into play. The kidneys retain HCO_3^- 3–4 mEq or mmoL/L being retained for every 10 mm Hg rise in $PaCO_2$. Significant HCO_3^- retention thus compensates for the chronic rise in $PaCO_2$, and helps to preserve the "balance". Retention of bicarbonate by the kidneys takes time; it probably starts 4–6 hours after the rise in $PaCO_2$, and is complete after 2–3 days. Compensation however can only occur up to a point—a rise in $PaCO_2$ more than 65 mm Hg is generally associated with a fall in pH below normal in spite of HCO_3^- retention. The degree of rise in HCO_3^- enables one to determine whether in a given patient the respiratory acidosis is acute or chronic. Uncompensated respiratory acidosis (respiratory acidemia) and compensated respiratory acidosis are illustrated in Figures 2 and 3, respectively.

Comparison of degrees of rise in HCO_3^- in vivo due to acute and chronic rise in $PaCO_2$ is illustrated in Figure 4.

A fall in $PaCO_2$ primarily due to alveolar hyperventilation leads to a compensatory fall in plasma HCO_3^-, the degree of

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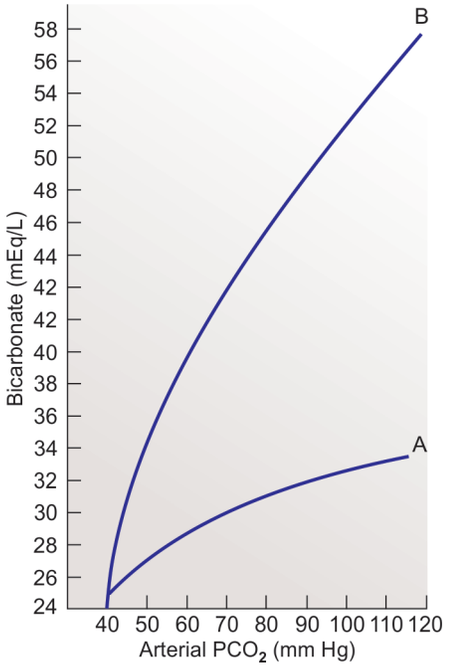

Fig. 4: Comparison curves showing rise in HCO_3^- levels in vivo with chronic and acute hypercapnia. A = rise in acute hypercapnia. B = rise in chronic hypercapnia, the curve in this case is higher and steeper than that in acute hypercapnia, because of retention of HCO_3^- by the kidney

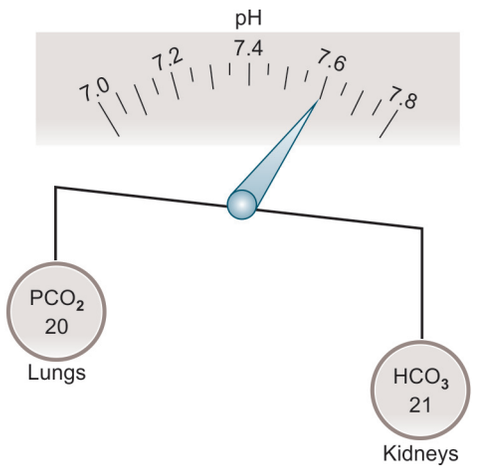

Fig. 5: Acute uncompensated respiratory alkalosis

fall approximating 0.1–0.3 mmoL/L for 1 mm Hg fall in $PaCO_2$. Acid-base balance in acute, uncompensated respiratory alkalosis is illustrated in Figure 5.

When primary metabolic problems produce a fall in HCO_3^-, metabolic acidosis results. When the pH falls to less than 7.35, metabolic acidemia results.

Metabolic alkalosis results following retention of HCO_3^- due to metabolic causes; metabolic alkalemia ensues when the pH rises to more than 7.45.

Primary metabolic changes in HCO_3^- result in secondary changes in $PaCO_2$, thus minimizing changes in the pH. Thus, metabolic acidosis stimulates the respiratory center,

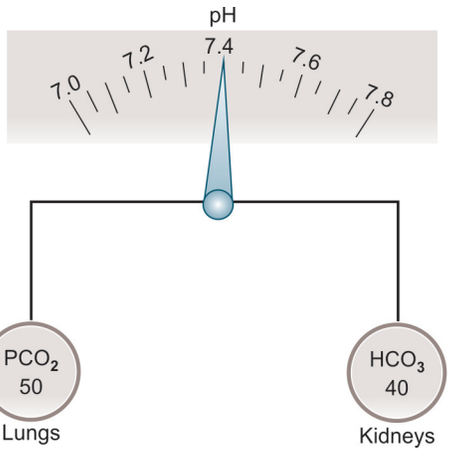

Fig. 6: Compensated metabolic alkalosis

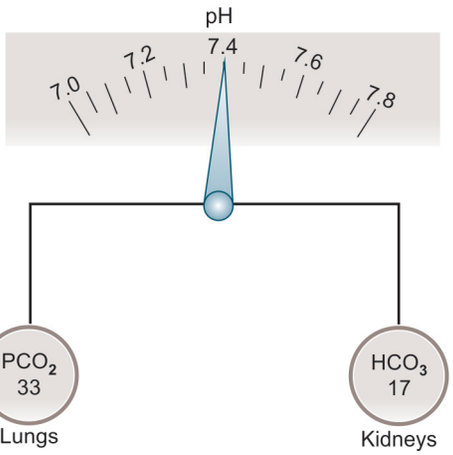

Fig. 7: Compensated metabolic acidosis

and the resulting hyperventilation reduces the $PaCO_2$. The degree of compensatory fall in $PaCO_2$ roughly equals 1.2 mm Hg for every 1 mmoL or mEq/L fall in HCO_3^- (or roughly equals 1.5 HCO_3^- content + 8). On the other hand, metabolic alkalosis depresses the respiratory center and produces a compensatory rise in $PaCO_2$, the degree of rise being 0.6–1 mm Hg for 1 mmoL or mEq/L rise in HCO_3^-. The expected $PaCO_2$ can also be considered as = 0.7 × HCO_3^- + 20 (±1.5). Figures 6 and 7 illustrate compensated metabolic acid-base disturbances.

MIXED ACID-BASE DISTURBANCES

Acid-base disturbances in critically ill patients are often due to both respiratory and metabolic problems occurring independently. A consideration of the clinical picture, the pH, $PaCO_2$ and HCO_3^-, invariably clarifies the diagnosis. The degree of compensation present in relation to HCO_3^- in primary respiratory disturbances, and the degree of compensation present in relation to $PaCO_2$ in primary metabolic problems, enables one to judge whether acid-base disturbances are due to mixed causes. The examples briefly quoted below help to give a more practical understanding of the problems involved.

A patient with chronic bronchitis emphysema deteriorated over a period of weeks, and was admitted to hospital in a critically ill condition with acute respiratory failure. The $PaCO_2$ was 82 mm Hg, PaO_2 34 mm Hg, pH 7.15, HCO_3^- 26 mEq/L. This patient obviously had respiratory acidosis ($PaCO_2$ 82 mm Hg). However, in a slowly deteriorating respiratory problem, the rise in $PaCO_2$ should have been offset by a rise in plasma HCO_3^- at a rate of 4 mEq/L for every 10 mm Hg rise in $PaCO_2$, i.e. approximately 40 mEq/L. Even in severe acute respiratory failure, the HCO_3^- should increase at a rate of 1 mEq/L for every 10 mm Hg rise in $PaCO_2$. The low HCO_3^- associated with the high $PaCO_2$ seen in this patient, is therefore due to an associated metabolic acidosis, possibly due to severe hypoxemia inducing a lactic acid acidosis.

Another patient with a history of diabetes and chronic bronchitis was admitted to hospital in a drowsy state. His pH was 7.21, $PaCO_2$ 42 mm Hg, PaO_2 50 mm Hg, HCO_3^- 14 mEq/L. He had ketosis in the urine with ketonemia. The above values pointed to the presence of metabolic acidosis; however, the comparatively high $PaCO_2$ (it should ordinarily have been 28 mm Hg), indicates an associated respiratory acidosis.

A frequently observed mixed acid-base disturbance in critical care units is a combination of respiratory acidosis and metabolic alkalosis in patients with chronic airways obstruction, who are hypokalemic due to the use of diuretics. The following example in a patient with the above problem is illustrative: pH 7.44; $PaCO_2$ 60 mm Hg; HCO_3^- 38 mEq/L; serum K^+ 3 mEq/L. The rise in the HCO_3^- significantly exceeds the maximum of 0.4 mEq/mm Hg rise in the $PaCO_2$. This is due to a hypokalemic metabolic acidosis.

A combination of respiratory acidosis and metabolic acidosis is often observed when respiratory failure due to alveolar hypoventilation, is combined with increasing hypoxia and poor tissue perfusion due to poor pump function. The following example is illustrative of this profile: pH 7.1; $PaCO_2$ 55 mm Hg; HCO_3^- 15 mEq/L. Instead of the expected rise in HCO_3^- due to a high $PaCO_2$, there is a fall in the HCO_3^- because of metabolic lactic acid acidosis induced by hypotension and poor tissue perfusion due to associated cardiac failure.

A combination of respiratory alkalosis and metabolic alkalosis is at times observed in hepatic failure. The latter causes tachypnea with respiratory alkalosis. If there is associated vomiting, or there is aspiration of gastric contents through a nasogastric tube, the loss of H^+, K^+ and Cl^- leads to an associated metabolic alkalosis. The following example is illustrative: pH 7.61; $PaCO_2$ 25 mm Hg; HCO_3^- 34 mEq/L.

A combination of respiratory alkalosis and metabolic acidosis may occur in septic shock and also in terminal acute liver cell failure. Both these conditions can cause tachypnea with respiratory alkalosis. The metabolic (lactic acid) acidosis is related to shock and poor tissue perfusion. The same combination is often observed in patients who are hyperventilated on mechanical ventilation (with resulting respiratory alkalosis), and who are hypotensive from shock or poor pump function (which causes lactic acid acidosis).

Box 1: Common causes of metabolic acidosis

1. Normal anion gap—
   - Diarrhea
   - Intestinal or pancreatic fistulae
   - Renal tubular acidosis
   - As compensation for respiratory alkalosis
   - Ureterosigmoidostomy
   - Infusion with fluids having high chloride content
2. High anion gap—
   - Lactic acidosis
   - Ketoacidosis (alcoholics, diabetics)
   - Renal failure
   - Poisonings (salicylates, acids, methyl alcohol, ethylene glycol)

Renal failure with excessive vomiting, or with a loss of gastric secretions from nasogastric aspiration, can result in a combination of metabolic acidosis and metabolic alkalosis, with the pH well within the normal range.

Arterial pH of blood gases and HCO_3^- levels should always be interpreted with reference to the history, clinical findings, and other investigations in every individual problem. Occasionally, the complexity of an acid-base disturbance is only apparent on a follow-up of the patient.

CLINICAL FEATURES AND MANAGEMENT OF ACID-BASE DISTURBANCES

Metabolic Acidosis

The diagnosis of metabolic acidosis rests on a clinical awareness of its presence in situations where it is a recognized complication. It should always be suspected in severe uncontrolled diabetes, in acute or chronic renal failure, in poisoning with acids, aspirin, or methyl alcohol, and in patients who have a continuing loss of HCO_3^- (as in diarrhea, or intestinal or pancreatic fistulae). Severe hypoxia, particularly when associated with poor tissue perfusion, is an important cause of metabolic acidosis due to accumulation of lactic acid. Poor tissue perfusion may be localized as in peripheral vascular disease, or generalized due to poor pump function, or to shock from any cause. Metabolic acidosis can also occur after cardiac arrest—the longer the period required for resuscitation, the greater the chances of increasing metabolic acidosis.

Metabolic acidosis is often divided into two groups: (1) normal anion gap and (2) high anion gap. The group with a normal anion gap is characterized by loss of HCO_3^-. This results in a replacement of Cl^- for the lost HCO_3^- to preserve electrical neutrality, and the increase in serum chloride causes a hyperchloremic metabolic acidosis. The group with the high anion gap is characterized by the addition of a fixed acid, e.g. lactic acid. The common causes of metabolic acidosis are

Box 2: Effects of acidemia

- Cardiovascular—
  - Decreased cardiac contractile function
  - Centralization of blood volume (venoconstriction and arteriolar dilatation)
- Hypotension
  - Decreased fibrillation threshold
  - Decreased cardiac sensitivity to catecholamines in severe acidemia
  - Less likelihood of conversion to sinus rhythm once fibrillation is established
  - Tachycardia
- Neurologic—
  - Obtundation and coma
  - Increased cerebral blood flow
  - Increased sympathetic discharge
  - Decreased responsiveness to circulating catecholamines (severe acidemia)
- Respiratory—
  - Increased minute ventilation
  - Dyspnea
  - Respiratory muscle fatigue
- Metabolic—
  - Inhibition of anaerobic metabolism
  - Hyperkalemia (inorganic acidemias)
  - Hyperphosphatemia

Source: Gauthier PM, Szerlip HM. Metabolic acidosis in the intensive care unit. Crit Care Clin. 2002;18(2):289-308.

summarized in Box 1 and the effects of academia are listed in Box 2.

Anion Gap

It is assumed that the negatively charged anions and the positively charged cations are equal for purposes of electrical neutrality. If so, then the unmeasured anions and unmeasured cations can be determined using the serum Cl^-, HCO_3^- and Na^+. The difference between the unmeasured anions and cations in the serum is termed the anion gap, and is equal to $(Na^+) - (Cl^- + HCO_3^-)$. The normal anion gap is 10 ± 4 mEq/L.[1] An increase of over 15 mEq/L in the anion gap is generally considered to be abnormal.

The serum anion gap is illustrated below in detail in Table 2.

Unmeasured anions + $(Cl^- + HCO_3^-) = Na^+$ + unmeasured cations

Thus, unmeasured anions-unmeasured cations (which constitute the anion gap) = $Na^+ - (Cl^- + HCO_3^-)$

The fall in HCO_3^- which characterizes metabolic acidosis is ordinarily considered to be due to: (1) titration with an endogenously produced organic acid, in which case the fall in HCO_3^- is not matched by a rise in Cl^- and the anion gap widens or (2) a loss of HCO_3^- [either from the gastrointestinal tract or the kidneys via the urine] in which case the fall in HCO_3^- is matched by rise in the Cl^- and the anion gap remains normal. Hence, the division of metabolic acidosis is into anion gap acidosis versus non-anion gap acidosis. The exception to be noted is that administration of hydrochloric acid results in normal anion gap.

Table 4: Serum anion gap

Unmeasured anions in serum (mEq/L)		*Unmeasured cations in serum (mEq/L)*	
Proteins	15	K^+	4.5
Organic acids	5	Ca^{++}	5.0
PO_4^-	2	Mg^{++}	1.5
SO_4^-	1		
Total	23	Total	11.0
The anion gap = 12 mEq/L			

Strict adherence to the above division, particularly in critical care medicine can lead to inaccuracies. The normal serum anion gap is chiefly composed of proteins, in the main albumin. Hypoalbuminemia is extremely common in critically ill patients and spuriously lowers the anion gap, thereby masking an underlying anion gap acidosis. Serum albumin should therefore always be measured in assessing acid-base disturbances. For every 1 g decrease in serum albumin below 4 g the serum anion gap should be corrected by 2.5–3 mEq/L. Hence, a serum albumin of 2 g would amount to an increase in the anion gap by 6 mEq/L.

Another important point of clinical relevance is to remember that in some cases of lactic acidosis, the anion gap may remain well in the normal range. In fact, the serum lactate may be quite elevated in the presence of a normal anion gap.[3] It is also important to note that the kidney can excrete many organic anions especially ketoacids, replacing them with Cl^-, thereby effectively reducing the anion gap. This chiefly is dependent on kidney function, in particular the glomerular filtration rate. The hypovolemic hyperglycemic, ketotic diabetic will present therefore with a high anion gap; on the other hand, the occasional diabetic ketonic patient who is euvolemic or who is being treated with intravenous fluid will present with a nonanion gap acidosis.

Other causes of reduced anion gap include paraproteinemias, an increase in unmeasured cations (Ca^+, K^+, Mg^+), and hyponatremia. The reason for a reduced anion gap in hyponatremia is unclear. In dilutional hyponatremia, the extra water (H_2O) in serum should decrease serum Cl^- as much as serum Na^+, leaving the anion gap unchanged. However, this is not necessarily the case; the Cl^- does not show an equivalent reduction as the Na in many cases of hyponatremia. Perhaps unmeasured cations like Ca^+ and Mg^+ may increase in the serum during hyponatremia, and the Cl^- remains comparatively elevated to provide electrical neutrality.

It should be noted that the concept of the anion gap rests on the assumption that unmeasured cations are rarely present in significant amounts. In fact, in critically ill patients it has been shown that unmeasured, unidentified cations are indeed present.[4] In these patients, the calculated anion gap would be much lower than the actual concentration of unmeasured anions, thus allowing an anion gap acidosis to masquerade as nonanion gap acidosis.

The concept of the anion gap though useful may in some instances be an imperfect measurement in the diagnosis of metabolic acidosis. The clinician should therefore never rule out the possible etiology of metabolic acidosis particularly in critically ill patients on the basis of the anion gap alone.

Stewart Method or Factor[5-8]

The classical approach to acid base disturbance has been challenged by Stewart because it ignores a principle of chemistry. which states that the H^+ concentration of an aqueous solution is determined by the dissociation of H_2O. These changes in H^+ occur not so much because of addition of H^+, but more from a shift in the equilibrium of the equation $H_2O \rightleftharpoons H^+ + OH^-$. Stewart showed that ($H^+$) is determined by only three independent variables—the strong ion difference (SID), the concentration of weak acids (mainly proteins) and PCO_2. According to the above concept, metabolic acidosis results either from alteration in the SID or total weak acid concentration. The SID is the net charge balance of all strong ions present in the system. By strong ions is meant ions that for all purposes are completely dissociated. Thus, SID = [Na + K + Ca + Mg + PO_4 – Cl – (lactate)].

The equation is often referred to as "apparent" SID or SIDa in order to emphasize that other unmeasured strong anions or cations may be present.[9] The normal value for SID is 40–42 mEq/L.

Again, according to the above concept neither hydrogen nor hydroxy ions are strong ions because H_2O is a weak electrolyte. HCO_3^- also is not a strong electrolyte because it can combine with other chemicals such as CO_2 or hydrogen. The principles of physical chemistry dictate that strong ions are inert, so that weak electrolytes like H_2O must alter their dissociation so as to maintain electrical neutrality. If therefore we give a patient sodium bicarbonate ($NaHCO_3^-$) serum HCO_3^- rises not because we have given HCO_3^-, but because of the addition of the strong cation Na^+, which causes the dissociation of H_2O to "shift" to the left resulting in fewer H^+ and hence to higher pH. Similarly in lactic acidosis, the cause of the acidosis is the strong organic ion, i.e. lactate and not the accompanying H^+.

In conclusion, though the traditional Henderson-Hasselbalch approach is generally sufficient to explain acid base disturbances in critical care medicine, the "Stewart approach", though complex, may help us to understand cryptic acidosis occasionally found in the intensive care unit (ICU). Unmeasured ions as identified by the Stewart method have been shown to predict mortality in a pediatric ICU better than either base excess, anion gap or lactate levels.

Clinical Features[5]

The clinical features of metabolic acidosis include—

- Hyperventilation due to stimulation of the respiratory center. This is first characterized by an increase in the depth of breathing, followed by an increase in the rate.
- An obtunded mental state—drowsiness progressing to deep coma.
- The smell of ketones in the breath points to diabetic ketoacidosis, while an ammoniacal smell in the breath is observed in uremic ketoacidosis.
- *The only manifestation of metabolic acidosis may be a progressive deterioration in the clinical state of a critically ill individual.* Metabolic acidosis impairs the function of most organs of the body, particularly the heart. This can be slow, insidious and unsuspected; if the acidosis remains uncorrected, it can lead to irreversible organ dysfunction and ultimately to death. Hence, the importance of measuring the arterial pH and blood gases in every critically ill patient.

Lactic Acid Acidosis[5]

This deserves special consideration as it is fairly frequent yet an often missed entity in critically ill patients in the ICU.

Lactic acid is a product of glucose metabolism. It is produced at an average rate of 1 mEq/kg per hour, the serum lactate levels being less than or equal to 2 mEq/L. Exercise can raise the serum lactate levels to 4 mEq/L. The lactate is metabolized by the liver and is used for gluconeogenesis or for energy production.

Etiology

The most common cause of lactic acid acidosis in ICU patients is shock, in particular cardiogenic shock, and septic shock. Sepsis can produce lactic acid acidosis in the absence of hypotension or the other clinical features of shock. This is due to the fact that oxygen supply is not commensurate with the increased demand for oxygen by the tissues (see Section Sepsis and Septic Shock). Multiple organ failure is also frequently associated with lactic acid acidosis—this is chiefly related to poor pump function, and to liver cell dysfunction. The rise of serum lactate in these conditions is due to the increased production of lactic acid, and decreased clearance of lactate by the liver. The latter may well be related to poor liver function consequent to hypoperfusion of the liver observed in shock.
Other important causes of lactic acid acidosis in the ICU are—

- Hypoxia. A low PaO_2 by itself may not induce a significant rise in serum lactate. In most patients with a low PaO_2, it is the associated presence of a low cardiac output that is responsible for a rise in lactic acid.
- Severe anemia. (Hb <5 g/dL) if not adequately compensated for by a hyperdynamic circulatory state can also lead to an increase in lactic acid levels in the blood.
- Severe liver cell dysfunction, particularly when associated with hypotension or shock can lead to lactic acid acidosis.

Rare causes of lactic acid acidosis in the ICU include—

- *Thiamine deficiency* This causes lactic acidosis by reducing the mitochondrial oxidation of pyruvate. The conversion of pyruvate to acetyl-coenzyme A is blocked by the lack of thiamine, and the pyruvate is converted to lactate. In critically ill patients, particularly in those with prolonged illnesses and with poor nutrition, thiamine deficiency must be suspected when the other more common causes

Box 3: Important causes of lactic acid acidosis in an intensive care unit (ICU) setting

- Shock of any etiology, particularly cardiogenic or septic shock
- Hypoxia, especially when associated with a low cardiac output
- Severe uncorrected anemia (Hb <5g/dL)
- Marked liver cell dysfunction, particularly when associated with shock or hypotension
- Thiamine deficiency
- Severe respiratory or metabolic alkalosis
- D-lactic acid acidosis often seen following small bowel resection or jejunoileostomy done for severe obesity
- Drugs, e.g. epinephrine or nitroprusside

of lactic acid acidosis do not seem to be responsible. A quick reversal of acidosis following thiamine injections points to the diagnosis of lactic acidosis due to thiamine deficiency.

- *Alkalosis* Increased serum lactate levels have been reported with severe metabolic alkalosis and respiratory alkalosis. This is probably due to extra production of lactate due to increased activity of pH dependent enzymes involving the glycolytic pathway. Severe alkalosis with a pH more than 7.6 is generally necessary for a rise in lactate levels, as a modest increase in lactate production is ordinarily metabolized by the liver, unless liver cell function is deranged, or there is associated hypoperfusion of the liver due to a poor circulatory state.
- *D-lactic acid acidosis*[5] The usual lactate produced in the body is a levo-isomer. The dextro-isomer is produced by bacterial fermentation of glucose in the colon. *Bacteroides fragilis*, other anaerobes, and Gram-negative organisms within the gut are also capable of inducing the formation of D-lactic acid. D-lactic acid acidosis is most frequently reported following small bowel resection and following jejunoileostomy for the treatment of severe obesity. The condition should therefore be suspected in a patient with an ill-explained metabolic acidosis with a high anion gap, particularly if there is a history of small bowel surgery or persistent diarrhea. A standard assay of lactate would not detect lactic acid, as it only measures the levo form of lactate. Special assays for D-lactic acid can only be done in highly specialized reference laboratories.
- *Drugs* Rarely the use of epinephrine and nitroprusside in the ICU may induce a lactic acid acidosis. The important causes of lactic acid acidosis in an ICU setting are listed in Box 3.

Diagnosis[11]

Lactic acid acidosis should be suspected whenever metabolic acidosis is associated with an increased anion gap.

The anion gap The anion gap in lactic acidosis is often more than 30 mEq/L. Even in patients with renal failure an anion gap more than 30 mEq/L should prompt one to suspect an additional lactic acidosis.

Estimation of lactate levels may vary in samples of arterial and venous blood. The venous blood lactate is higher because it represents lactate production, while arterial blood lactate is lower as it probably represents effect of both production and hepatic clearance. In patients with a Swan-Ganz catheter in situ, samples from the pulmonary artery are probably more representative of blood lactate levels. There is a good correlation in lactate levels in blood drawn from the pulmonary artery, and that drawn from arterial blood.

Treatment[5,12]

In the final analysis, treatment should be directed toward the cause. In emergency situations, it is vital to temporarily correct a severe acidosis and then deal with its root cause, otherwise death may result. It is wrong to await results of laboratory investigations in desperate situations where the clinical picture obviously points to severe metabolic acidosis. In such situations, acidosis is corrected by administering 75–100 mL of 7.5% $NaHCO_3$ as a bolus dose. Further, administration is guided by laboratory reports.

Ordinarily a pH of 7.25 or less deserves prompt correction. The amount of HCO_3^- in mEq required to correct metabolic acidosis is given by either of the two formulae given below—

1. Sodium HCO_3^- to be given = Body weight (kg) × 0.3 × base deficit.
2. Sodium HCO_3^- deficit = 0.5 × weight (kg) × (desired HCO_3^- -serum HCO_3^-).

The usual recommendation is to give one half of the HCO_3 deficit as an IV bolus, and to replace the remaining deficit over the next 4–6 hours. It is best not to be over-reliant on formulae but to administer ($NaHCO_3$) at a frequency and dose, which keep the arterial pH above 7.3.

In the presence of an associated respiratory acidosis it is important to first correct the respiratory acidosis, and then tackle the metabolic acidosis. ($NaHCO_3$) given intravenously to a patient with respiratory acidosis induces further CO_2 production and this could further increase the degree of respiratory acidosis. When the pH is very low in combined respiratory and metabolic acidosis, measures to correct both can be undertaken simultaneously.

Risks of sodium bicarbonate therapy[12] There is some degree of risk and therefore some degree of controversy on when to use $NaHCO_3$ for the correction of metabolic acidosis. This is because $NaHCO_3$ can produce undesirable effects which include hyperosmolarity, fluid overload due to large quantities of Na^+ in the $NaHCO_3$, hypokalemia, hypocalcaemia, and increased serum lactate levels. At times hypotension and a reduced cardiac output have been observed, probably due to calcium binding by the HCO_3^-. It is also obvious that an ongoing metabolic acidosis will remain uncorrected as soon as the administration of $NaHCO_3$ is stopped or reduced, because the cause of acidosis remains uncorrected. Alkali ($NaHCO_3$) stimulates

6-phosphofructokinase activity and organic acid production. This is not helpful in the management of lactic acid acidosis and ketoacidosis.[13] These effects limit the alkalizing effects of HCO_3^-. However, the alkali effect on 6-phosphofructokinase may help in partial regeneration of depleted adenosine triphosphate (ATP) stores in vital organs thereby improving organ function.

Theoretically, the CO_2 produced by the administration of HCO_3^- may partly diffuse into the RBCs and combine with the H_2O to form carbonic acid, thus adding to the H^+ load. In practice, however, we have rarely encountered problems with the administration of $NaHCO_3$. The most frequent side-effects to be looked out for are hyperosmolarity, hypokalemia, hypocalcemia and fluid overload. These can all be corrected by timely measures. We feel that this controversy in the use of $NaHCO_3$ is unnecessary, and that its advantages far outweigh the possible drawbacks. Its use is particularly gratifying when poor pump function is associated with metabolic acidosis. A restoration of pH toward normal leads to improved pump function, increase in systemic blood pressure and improved perfusion to the tissues.

Alternative alkalizing agents[12] Concern over the production of CO_2 following the use of $NaHCO_3$ led to the development of carbicarb, which consists of equimolar concentration of $NaHCO_3$ and sodium carbonate. Carbicarb limits, but does not eliminate the generation of CO_2. The risk of hyperosmolarity and hypervolemia remain.

Another CO_2 consuming alkalinizing agents is tris-hydroxymethyl aminomethane (THAM), a commercially available solution of 0.3 N tromethamine. It is not more clinically efficacious than $NaHCO_3$ has a number of serious side effects and is not in use.

Metabolic Alkalosis

The suspicion of this acid-base disturbance rests on an awareness of its likely occurrence in certain pathological conditions. Metabolic alkalosis is very frequently encountered in patients under critical care, as the four most important causes are vomiting (or nasogastric aspiration), the use of diuretics, the use of corticosteroids, and hypokalemia—all these factors being very frequently encountered in critical care medicine.[14,15] Galla and Luke[16] report an associated mortality of 40% when the arterial pH rises above 7.55. It is probably the gravity of the underlying illness, which contributes to this mortality. The danger with metabolic alkalosis is related to its ability to sustain itself in spite of correcting the underlying etiological factor. This is attributed to Cl^- depletion, which limits HCO_3^- excretion in the urine by promoting its reabsorption, and reducing its secretion into the renal tubules.

Etiology

- Vomiting or nasogastric suction is an important cause of metabolic alkalosis. Gastric juice contains 50–100 mEq/L of H^+ so that loss of gastric contents leads to significant H^+ loss. There is also an associated loss of Cl^-, Na^+, and potassium, as well as volume depletion due to H_2O loss.
- Diuretics, in particular furosemide, produce alkalosis chiefly through the loss of Cl^- and potassium via the urine. Cl^- follows Na^+ and H_2O during diuresis; the Cl^- that is not reabsorbed is replaced by HCO_3^-. The increased HCO_3^- reabsorption maintains or enhances the alkalosis. Increased K^+ loss in the urine leads to an increase in the H^+ secretion into the distal tubules, probably in an attempt to reabsorb K^+, and replace it with H^+ in the tubular fluid.[16] Magnesium is also lost in the urine during diuresis and this promotes K^+ loss through mechanisms not clearly understood. A decrease in extracellular volume probably contributes to alkalosis by increasing the concentration of HCO_3^- in the serum. A decrease in circulating volume also stimulates aldosterone release, and promotes the loss of K^+ and H^+ in the distal tubule. Thus, the importance of correcting the Na^+, K^+ and Cl^- loss as well as replenishing volume in management is self-evident.
- Administration of excess alkali either orally or through IV use promotes metabolic alkalosis. This is particularly observed when renal dysfunction prevents excretion of HCO_3^-, or when there are associated electrolyte (e.g. Cl^- depletion), which interfere with HCO_3^- excretion by the kidneys. Over-enthusiastic use of IV $NaHCO_3$ for the correction of metabolic acidosis can produce a dangerous swing to metabolic alkalosis. Massive blood transfusions (due to citrate in the blood), are also reported to cause a significant metabolic alkalosis.[17]
- Metabolic alkalosis occurs during corticosteroid therapy, in patients with adrenocortical hyperfunction, in aldosteronism, and it almost always complicates a well-marked hypokalemia.

Box 4: Common causes of metabolic alkalosis

- Vomiting or nasogastric aspiration
- Use of diuretics, particularly furosemide
- Excessive administration of alkali [orally or intravenous (IV)], particularly in the presence of associated renal dysfunction or electrolyte abnormality
- During corticosteroid therapy in patients with adrenocortical hyperfunction, aldosteronism, especially in the presence of well-marked hypokalemia

The common causes of metabolic alkalosis are given in Box 4.

Clinical Features

It is remarkable, how silent metabolic alkalosis can be. Severe alkalosis (serum HCO_3^- >40 mEq/L and pH >7.6) can cause mental obtundation, seizures, cardiac dysfunction and cardiac arrhythmias. Ventilation may be depressed (so that the $PaCO_2$ is secondarily raised), but this is not always the case. Marino[18] believes that the infrequency or lack of hypoventilation in metabolic alkalosis is related to the baseline activity of the

peripheral chemoreceptors, through which metabolic acid-base disorders chiefly exert their effect on ventilation. Under normal conditions the peripheral chemoreceptors have a low activity with a low "input" from the chemoreceptors to the brainstem respiratory centers. There is thus very little scope for alkalosis to further inhibit activity. On the other hand, acidosis stimulates these receptors, resulting in an increased "input" from the receptors to the respiratory centers, and thus causing hyperventilation.

It is also worth noting that a metabolic alkalosis shifts the oxygen dissociation curve to the left, thus reducing delivery of oxygen to the tissues. In a critically ill patient who already has a low PaO_2, a sudden shift of the oxygen dissociation curve can precipitate a further sharp fall in the PaO_2 and PvO_2. If pump function is poor and the patient already has a low PvO_2 (due to a low cardiac output), then the further fall in PaO_2 can have disastrous consequences.

Management

This is directed to the underlying etiology. Almost always (particularly in ICU patients), metabolic alkalosis is chloride responsive, and the Cl^- should be replaced in the form of normal saline. This also permits adequate replenishment of fluid loss. Hypokalemia also needs to be corrected by an infusion of KCl (20–40 mEq or more) in a dextrose infusion. It is important to note that uncorrected hypokalemia can perpetuate metabolic alkalosis. In patients with mineralocorticoid excess, aldactone helps to correct the hypokalemia and restore acid-base balance. When magnesium levels are depleted, magnesium should be replaced, thus allowing for easier correction of hypokalemia.

The volume of 0.9% saline necessary for correction of metabolic alkalosis can generally be gauged by clinical assessment of the degree of fluid loss, and the degree of electrolyte disturbances. The formula given below[18] is often used for estimating the Cl^- deficit—

Chloride deficit = 0.27 × weight (kg) × (100-present Cl^- in mEq/L)

Volume of saline to be administered (L) = Cl^- deficit/154*

(*The Cl^- present in 1 L N saline = 154 mEq).

Clinical judgment should never be replaced by didactic formulae and it is best to rely on the former rather than on the latter.

Use of Hydrochloric Acid

We have never found it necessary to use hydrochloric acid to correct metabolic alkalosis. It may however be used in rare instances where saline and potassium replacement are ineffective in correcting a severe metabolic alkalosis. The amount of HCl required is determined by the H^+ deficit.[19]

Hydrogen ion deficit (mEq) = 0.5 × weight (kg) × (present HCO_3^- - desired HCO_3^-)

Volume (L) of 0.1N HCl = H^+ deficit/100*

Volume (L) of 0.25N HCl = H^+ deficit/250*

Infusion rate = 0.2 mEq/kg/hour

*mEq of H^+ per liter of solution.

It is perhaps best to use a 0.1N HCl solution. However, when volume needs to be restricted, 0.25N HCl may be preferred. The infusion is best given through a central line, as if given peripherally it can cause a thrombophlebitis. Though we have never used an IV HCl solution for metabolic alkalosis, it has been proven to be safe and effective.[19] Other Cl-containing acids such as ammonium chloride (NH_4Cl) solutions and arginine hydrochloride have been used to correct metabolic alkalosis, but are best avoided. Arginine hydrochloride can cause severe hypokalemia in patients with renal dysfunction. NH_4Cl can result in high ammonia levels with possible toxic effects particularly in patients with liver cell dysfunction.

Hemofiltration

Continuous arteriovenous hemofiltration is valuable in the management of severe metabolic alkalosis with markedly increased extracellular volume. A reduction of H_2O content through continuous hemofiltration should be combined with judicious administration of normal saline and potassium in dextrose. The H_2O loss through ultrafiltration should be greater than the fluids infused, so as to correct the increase in extracellular volume.

Respiratory Acidosis

This is due to a rise in the $PaCO_2$ of arterial blood; it complicates acute and chronic respiratory failure. The clinical features, diagnosis and management have been dealt with in an earlier chapter (see Chapter Acute Respiratory Failure in Adults).

Respiratory Alkalosis

This results from alveolar hyperventilation with a fall in the arterial $PaCO_2$, and in the carbonic acid content of plasma. It is common in hysterical or functional states, and in patients who are over-ventilated while on ventilator support. It can also occur because of hyperventilation produced by brainstem lesions. The recognition and diagnosis of respiratory alkalosis in patients on mechanical ventilation has been dealt with separately (see Chapter Mechanical Ventilation in the Critically Ill).

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SECTION

12

Nutritional Support in the Critically Ill Adult

- Nutritional Support in the Critically Ill Adult

CHAPTER 42

Nutritional Support in the Critically Ill Adult

GENERAL CONSIDERATIONS

Good nutrition is often vital for survival in a critical illness. In poor developing countries, many illnesses unfold against the background of malnutrition. The chances of a patient succumbing to a critical illness increase with the degree of malnourishment present prior to the illness. A critically ill patient is often hypercatabolic from infection, injury and sepsis, and is very prone to develop malnutrition even if reasonably well nourished to start with. Specific or multiple organ failure compounds the issue. These patients have an increase in energy requirements, and because of metabolic abnormalities have problems in the handling of energy substrates provided to them. Clinically, they rapidly lose body weight, and in particular show a marked loss in the lean body mass. Nutritional support is therefore vital in the management of any critical illness. The more prolonged and more catabolic (or hypermetabolic) the illness, the greater the need and importance of nutritional support for survival.

In the large public and municipal hospitals of our country, in my opinion, over 50% patients suffer from protein or calorie malnutrition. The cause of malnutrition in affluent groups is related to background disease, and occasionally to fads and fancies in eating habits. During the course of a critical illness, a loss of lean muscle mass of 10% is significant, a loss of 20% is critical, and a loss of 30% or more is generally lethal.[1] In a critical illness, absence of adequate nutritional support leads to a form of starvation. Skeletal muscle is therefore soon catabolized for gluconeogenesis and energy. Additional endogenous nutritional support is provided by important proteins synthesized by metabolically active tissue. These proteins have a rapid turnover and include liver enzyme proteins, renal tubular enzymes and proteins formed in the gastrointestinal mucosa.[1] Endogenously derived nutritional support enables a critically ill individual to adapt to the stress of a critical illness, and provides the patient with an additional source of energy. The adaptation however is of benefit only in mild to moderate, short-lasting illnesses. In a severely catabolic long-lasting critical illness, the above response becomes maladaptive, and may well contribute to failure of individual or multiple organ systems, and thus be responsible for both increased morbidity and mortality.

PRINCIPLES OF NUTRITIONAL MANAGEMENT IN THE CRITICALLY ILL

The principles of nutritional support and management have evolved significantly over the last 20 years. These include changes in nutritional assessment, guidelines in total energy provided; in nutritional requirement related to specific diseases and in immune-enhancing enteral nutrition. Malnutrition, which often evolves during the course of a critical illness is known to be associated with serious complications, such as sepsis and pneumonia leading to a worsening outcome and often death.[2] The importance of good nutritional support in management needs repeated emphasis.

The society of Critical Care Medicine and the American Society of Parenteral and Enteral Nutrition convened an expert panel to establish guidelines for providing and assessing nutritional support therapy in adult critically ill patients.[3] In the past, nutritional support in critically ill patients was regarded as adjunctive care designed to preserve lean body mass, maintain immune function and prevent metabolic complications. The current recommendation of these societies published in 2007 is that nutritional support should be considered as nutritional therapy directed toward

attenuating the metabolic response to stress, preventing oxidative injury and improving the immune response.[3]

The basic principles of nutritional therapy in the critically ill patients are briefly enumerated below—

- Enteral nutrition (use of the gut for nutrition) has more advantages compared to parenteral nutrition (nutrients administered intravenously). The latter should therefore be offered only if the gut does not work, and hence cannot be used. When it is possible to provide even part of nutritional support via the gut, one should do so; parenteral nutrition is then used as a supplement to feeding via the gut. As a corollary to this principle, the importance of maintaining the structural and functional integrity of the gut cannot be overstressed.
- Conventional parenteral or enteral nutritional support has not been shown to always produce an anabolic effect in malnourished critically ill patients. For example, patients with fulminant Grade IV tetanus (one of the most catabolic of all diseases), even if they survive, lose a great deal of body weight and lean muscle mass in spite of excellent nutritional support (3,000 calories, with over 100 g proteins). The objective of parenteral nutrition in a critical illness is therefore to blunt or reduce the effects of hypercatabolism.

  Till the early nineties, it used to be felt that the nutritional requirements of highly catabolic critical illnesses should be met by an increasing and excessive supply of calories. Patients in critical care units thus often received over 3,500–4,500 calories/day. Today, this concept has been revised, and nutritional support is devised to provide a caloric intake of only 1,500–2,100 calories/day to most critically ill patients in the intensive care unit (ICU). Only exceptional problems require a larger caloric intake. This revision is related to two observations: (1) Excessive caloric intake as already mentioned, does not prevent weight loss or loss of lean muscle mass; (2) Overzealous calorie administration contributes to a number of deleterious side effects. These include hyperglycemia, excessive carbon dioxide production, overhydration with peripheral and pulmonary edema, hepatic dysfunction with steatosis and an increased incidence of noncatheter-related infections.
- Most critical care units would prefer to initiate nutritional support early rather than late in the natural history of a critical illness. This is based on the logic that it is perhaps easier to prevent or reduce the complications of starvation, than to treat them after they have occurred. Early nutritional, and in particular early parenteral nutritional support, may however be overdone. Cost in our country is an important factor, and parenteral nutrition is extremely costly. The use of preoperative parenteral nutrition in patients with mild malnutrition is of doubtful efficacy and may not result in any overall benefit. On the other hand, nutritional supplementation prior to surgery in severely malnourished patients clearly reduces the incidence of postoperative complications.[4]
- Nutritional support should always be individualized both with regard to the appropriate mode of administration, and the nutritional requirements of each patient. This will depend on the nature of the disease and the nutritional state of the patient.

  A little of "this" added to a little of "that" does not constitute good nutritional support; it only constitutes bad medicine.
- Nutritional support to a patient should be monitored with regard to the adequacy of the nutritional regime, response to treatment and possible side effects.

CLINICAL EFFECTS OF NUTRITIONAL DEPRIVATION

The deleterious clinical effects of poor or absent nutrition include wound dehiscence, poor healing, breakdown of surgical anastomosis, and poor immune response to infection. Poor host resistance has been related to a deficiency in proteins and in essential amino acids. Complicating sepsis or infection is thus an important feature in patients who have received poor nutritional support.

Non-specific effects are also observed in the central nervous system. These include apathy, drowsiness, and inability to clear secretions in the upper respiratory tract. The cause of these effects is unclear. They may be related to diminished energy supply to the brain, resulting in impaired function, or to toxic effects produced by the accumulation of products from the breakdown of muscle protein. Starvation produces an alteration in the amino acid profile, and this may in turn affect the neurotransmitter profile within the brain, and thereby alter central nervous function.

The effect of nutritional deprivation is chiefly on lean muscle mass. More and more muscle is used for neoglucogenesis. Ultimately, even the intercostals, the diaphragm and the upper abdominals are compromised, and there is insufficient muscle mass to perform the work of breathing. This is one reason why it is difficult to wean patients after a very prolonged period of ventilator support. In some instances, the muscles are so atrophic that even with hyperalimentation, muscle mass does not increase sufficiently for the patient to breathe on his own.

Berk is of the opinion that starvation in the presence of sepsis can contribute to multiple organ dysfunction and failure, particularly of the liver and kidneys.[1] It was pointed out earlier that rapidly turning over proteins (such as enzymatic proteins produced by liver cells and kidney tubules), are used for gluconeogenesis to provide energy in patients with poor nutrition. It has been postulated that a significant contribution to hepatic and renal dysfunction may be due to cannibalization of important functional elements for gluconeogenesis.[1]

METABOLIC EFFECTS OF NUTRITIONAL DEPRIVATION IN "INJURY" (SEPSIS, TRAUMA, CATABOLIC CRITICAL ILLNESSES)

The energy consumption pattern following "injury" is altered, an increased proportion of energy (caloric) needs being derived from protein breakdown, rather than from the utilization of carbohydrates and fats. The requirement for an increased protein intake in these circumstances is obvious. The reason for altered utilization of energy substrates is due to glucose intolerance that develops as a response to hypercatabolic critical illnesses. Thus, during stress, the maximal oxidation rate of glucose is only marginally increased to 3–5 mg/kg per minute. The reasons for glucose intolerance include elevated levels of catecholamines and other catabolic hormones, increased glucagon levels with a high glucagon-insulin ratio, and a poor uptake and utilization of glucose by tissues, in particular by the liver. In fact, there exists a state of "insulin resistance" during the "stress" produced by a critical illness. The inability to take up and utilize glucose has been thought to be related to both receptor and postreceptor defects in tissue cells. Postreceptor alterations in glucose metabolism may involve steps responsible for glucose uptake (transport and phosphorylation), glycogenolysis, glycolysis or oxidation. If exogenous glucose is not supplied (as in starvation), muscle, brain and other tissues will use for energy purposes glucose derived from muscle protein breakdown (gluconeogenesis), or ketone bodies derived from free fatty acids liberated by lipolysis. In addition, muscle is capable of using the branched-chain amino acids (leucine, valine and isoleucine) for energy directly, without the intervention of glucose.

In the metabolic pattern produced by "injury" (e.g. sepsis, severe trauma), in addition to glucose intolerance, there is an inability of the liver to manufacture ketone bodies, and an impairment in the utilization of fatty acids for energy. There is thus a marked increase in the breakdown of lean body mass to meet increased energy needs, and to provide the necessary calories for function of vital organ systems.

The association of fever, tissue damage, blood, plasma and protein loss, compound the metabolic problems in critically ill patients. Additional metabolic requirements secondary to the increased work of breathing may deprive important organ systems of necessary energy substrates, the latter being partially diverted to muscles of respiration. Fever significantly adds to caloric needs. Each degree of fever causes a 10–13% increase in oxygen consumption,[1] necessitating an increase in calorie requirement.

NUTRITIONAL ASSESSMENT

How does one assess nutrition or rather the degree of malnutrition in a critically ill individual?

- The general appearance of the patient with emphasis on the presence of wasting of the upper body and of the muscles mass, particularly of the upper limbs is a quick clinical method of assessing the nutritional state.
- A weight loss of 10th or 10% of usual weight is clinically important, weight loss of 20–30% suggest moderate protein calorie malnutrition; a weight loss of 30% or more is to be considered as severe protein calorie malnutrition and is often associated with death. Unfortunately, consideration of the body weight in many critically ill individuals is vitiated because of the frequent occurrence of salt and water retention and fluctuations in fluid electrolytes balance.
- Anthropometrics (measurement of triceps skin fold thickness and mid-arm circumference) are reasonably accurate reflections of the lean muscle loss as even if edema is present, it is not generally present in the upper limbs.
- A patient weight less than 80% of the ideal body weight (IBW) or body mass index (BMI) less than 18.5 indicates moderate malnutrition. A body weight less than 75% of IBW or a BMI less than 16 kg/m^2 signifies severe malnutrition. The urgency and degree of nutritional support is obviously much greater in those with significantly lowered body weight and BMI.
- Malnutrition in critically ill individuals is closely mirrored in the total lymphocyte count and the skin test reactivity. A total lymphocyte count <1,000/mm^3 and a loss of delayed skin sensitivity to common antigens (a measure of impaired cellular immunity) is frequently associated with malnutrition.[5]
- Subjective global assessment (SGA) evaluates nutritional states by using clinical parameters—history, physical findings and symptoms. The SGA determines if: (1) the poor nutritional state is related to poor ingestion, poor digestion or malabsorption; (2) if the degree of malnutrition has affected organ function and body composition; (3) whether the patient's illness or disease has influenced nutrient requirements.
- History and physical examination. Important features in history include the medical and surgical background of current and past illness with specific reference to conditions that could impair ingestion, digestion or absorption of nutrients.

Physical examination should carefully seek evidence of protein calorie malnutrition, deficiency of essential fatty acids, anemia, vitamin deficiencies and deficiency of trace elements.

- Biochemical parameters—
  - Serum proteins and serum albumin levels. The serum albumin level in particular is a good marker or predictor of malnutrition, as it provides an index of the visceral and somatic protein stores in a critical illness. There are however a few important points to be remembered in interpreting low serum albumin levels. A fall in the serum albumin may be brought about by rapid intravenous hydration or an overhydrated state, rather than by a change in the nutritional status. Again, low albumin levels may occur with increased catabolism, decreased synthesis (as in liver disease),

or in increased loss (as in burns, large wounds, in feces or in urine), even when the patient has been adequately nourished. Finally, even if a low serum albumin level in a critical illness serves as a marker for the initial nutritional state, it does not serve as a marker if the nutritional state has improved following nutritional support. This is because serum albumin has a half-life of 20 days and the plasma level does not rise significantly for 4–5 weeks following nutritional repletion.

- Estimation of levels of serum transferrin, thyroxin-binding prealbumin, retinol-binding protein and fibronectin. Lowered levels of transferrin (half-life 8 days), thyroxin-binding prealbumin (half-life 2 days), retinol-binding protein (half-life 12 hours), and fibronectin (half-life 12 hours), have all been used in well-equipped laboratories as indices of malnutrition. A significant rise in these proteins following repletion is observed fairly early and points to an improved nutritional state. Prealbumin is measured by many laboratories. It is a transport protein synthesized by the liver and transported in the serum as a complex of retinal binding protein. It is a sensitive indicator of protein deficiency and of improvement in protein status following good nutrition. We have never used these esoteric markers for reasons of cost. Though the above biomarkers may be of use, they cannot replace a holistic evaluation of the patient based on history, clinical examination, and on simple laboratory data.
- Estimation of 24 hours urinary urea nitrogen excretion and determination of nitrogen balance. This test evaluates somatic protein status. It provides a good index of protein breakdown, and if the protein intake is known, the nitrogen balance can easily be calculated.

$$\text{Nitrogen Balance} = \text{Nitrogen Intake} - \text{Nitrogen Excretion}$$

$$= \frac{\text{Protein intake}}{6.25} - (\text{24 hours urinary urea nitrogen excretion} + 4)$$

The 4 g are added to the urinary nitrogen loss to account for fecal and other losses in patients fed via the gut. Fecal loss of nitrogen is often much less. It is near zero to 1 g when patients receive total parenteral nutrition (TPN) even when there is diarrhea.[6]

A urinary loss of less than 6 g is normal; loss of 6–12 g/day is mild; loss of 12–18 g is moderate and more than 18 g/day indicates severe catabolism. Since 1 g of urea nitrogen is equivalent to 6.25 g of nonhydrated protein, a total loss of 16 g nitrogen would mean that about 100 g protein needs to be given to maintain nitrogen balance.

The above concept holds as long as the urine is a major source of nitrogen loss. It does not hold in patients who lose large quantities of nitrogen through the gut as in diarrhea, or through the surface of extensive weeping wounds. Nitrogen balance cannot be correctly evaluated by this equation in patients with nitrogen retention due to renal insufficiency.

- Estimation of fecal fat over 24 hours. An excretion of more than 5–7 g of fat in the stools following a diet containing 75 g of fat is an important marker for malabsorption.

In conclusion, the statement issued by the National Institute of Health, American Society for Parenteral and Enteral Nutrition and the American Society for Clinical Nutrition is worth quoting—

"There is no gold standard for determining nutritional status because: (1) there is no universally accepted clinical definition of malnutrition; (2) all current assessment parameters are affected by illness and injury; (3) it is difficult to isolate the defect of malnutrition from the influence of the disease in clinical outcome, and (4) it is not clear which of the commonly used nutrition assessment techniques is the most reliable because of the paucity of comparative data."

Perhaps, the most commonly used markers are weight loss, serum albumin, Subjective Global Assessment (SGA) and stress levels [as judged by the Acute Physiology and Chronic Health Evaluation (APACHE) II score] as they are both simple to measure and generally accepted.

TIMING FOR NUTRITIONAL SUPPORT

Theoretically speaking, any critically ill patient who is unable to take adequate nutrition should promptly receive nutritional support. There are however important points to consider before initiating nutritional support, and in particular parenteral nutritional support.

- Nutritional deprivation, in an illness lasting for a few days, is not likely to produce problems or complications. The number of days that a patient can withstand inadequate nutrition depends on age, previous nutritional status, previous state of health, and the presence of sepsis or trauma. An adult under 60 years of age, and in a previously good nutritional state, will withstand 14 days of poor nutrition in a moderately catabolic illness, without demonstrating a measurable defect. For patients between 60–70 years, this tolerance drops to 10 days, and for those more than 70 years, to less than 7 days.[1] *Nevertheless, one does not await the effects of starvation before starting nutritional support.*
- The excessive cost of parenteral nutrition precludes its unnecessary use during short periods of inadequate nutrition in a critical illness.
- Nutritional support, and in particular parenteral nutritional support, has inherent risks and can cause dangerous iatrogenic complications. These risks may well outbalance the risk of poor nutrition that is anticipated to last just under a week.
- For improved outcomes, *current recommendations advocate early nutritional support in patients critically ill in the ICU.*[3] Our policy is to initiate support promptly if enteral feeds are feasible. If enteral feeds are not feasible, or provide only a portion of the patient's nutritional requirements, we initiate parenteral nutrition within

3–5 days depending on the severity of the catabolic nature of the illness.

- *In an acute, hypercatabolic critical illness, stabilization of hemodynamics, and correction of fluid, electrolyte and acid-base balance take precedence over nutrition.[7] The latter can be started once the patient is reasonably stable in relation to the above mentioned vital parameters.*

INDICATIONS FOR PARENTERAL NUTRITION

Parenteral nutrition is indicated in patients in whom the gut does not function, or in those who undergo any form of treatment which precludes the use of the gut for the foreseeable future. Parenteral nutrition improves the outcome in the short bowel syndrome, enterocutaneous fistulae with a large leak greater than 500 mL from the fistulae, major burns, and acute tubular necrosis. Nutritional support is also of value in necrotizing or suppurative pancreatitis (till such time as the gut can be used), sepsis, prolonged ileus from any cause, stomal dysfunction after surgery, and in large wounds causing loss of proteins from the wound surface. Nutritional support is often offered to selected patients with cancer and to malnourished patients as a preparation for major surgery. Parenteral nutrition may be a supplement to enteral nutrition in many of these problems, so that caloric requirements and adequate protein intake are ensured. In many instances where the gut does not work or cannot be used, TPN is employed.

INDICATIONS FOR ENTERAL FEEDING

Patients with a functioning small bowel, who for any reason cannot take food orally, or who cannot meet their nutritional requirements, are given special supplements and/or tube feedings. The important indications, contraindications and further details of enteral nutrition are discussed later in this chapter.

Summary of evidence-based guidelines for nutrition support is listed in Box 1.

Box 1: Summary of evidence based guidelines for nutrition support

- Enteral nutrition is preferred over parenteral nutrition for critically ill patients who require nutrition support
- Bowel sounds are not required for the initiation of enteral feeding
- Immune modulating enteral formulations should be used for critically ill patients on mechanical ventilation but with caution in patients with severe sepsis
- Patients with ARDS and severe acute lung injury require enteral feeding containing anti-inflammatory lipids (i.e. omega-3 fish oil) and antioxidants
- Antioxidant vitamins and trace minerals, specifically containing selenium, should be given to all critically ill patients receiving nutritional therapy
- Enteral nutrition regimens not containing glutamine should be supplemented with glutamine in burns, trauma and critical illness
- Protocols to promote moderately strict control of serum glucose levels (110–150 mg/dL) when providing nutrition support are recommended

Source: Adapted from McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). J Parenter Enteral Nutr. 2009;33(3):277-316.

NUTRITIONAL REQUIREMENTS

Caloric Requirements

On an average, most critically ill individuals expend and therefore need 25–35 kcal/kg IBW per day. The resting metabolic expenditure can also be estimated by using the Harris-Benedict (HB) equation.[8] This formula or equation is as follows—

In Males: HB = 66.5 + 13.7 W + 5 H – 6.8 A
In Females: HB = 66.5 + 9.6 W + 1.7 H – 4.7 A
where W = Weight (kg); H = Height (cm); A = Age

The caloric requirement increases with the stress and catabolism of illness. Calvin Long's stress factors[9] take the catabolism of illness into consideration. Thus, the caloric requirement is as follows—

1.3 × HB for sepsis or uncomplicated major surgery

1.5 × HB for complicated sepsis (with organ failure) and burns <20%

2 × HB for burns >20%

We are of the opinion that it is quite unnecessary to use either the Harris-Benedict equation or the Calvin Long's "stress factors". Predictive equations can be notoriously unreliable in critically ill individuals[10] and the use of "corrective stress factors" invariably overestimates the caloric requirements of critically ill patients.

It is best to initially administer 25 kcal/kg per day in which total kilocalories in the day are split into 20% protein, 30% fats and 50% carbohydrates. Current recommendations in ICU patients are to apportion 60–70% of nonprotein calories as carbohydrates and 30–40% as fat. Proteins and carbohydrates provide 4 kcal/g, and fats provide 9 kcal/g (Table 1).

Carbohydrates

These are important and provide ready fuel for energy. Excessive glucose administration however has the following disadvantages—

- It increases norepinephrine secretion; this in turn increases energy expenditure, glucagon secretion and insulin resistance.
- Glucose is poorly utilized in sepsis and other catabolic states. Excessive glucose and carbohydrate administration will thus lead to severe hyperglycemia, particularly in diabetics.[11]

Table 1: Caloric requirement in a critically ill adult

Nutrient	*Quantity*	*Percentage of total calories*	*Initial requirement for 60 kg adult*
Total calories	25 kcal/kg/day	100	1500 kcal/day
Protein, peptides	1–1.75 g/kg/day	15–25	60–70 g/day 240–280 kcal/day
Carbohydrates	3–3.5 g/kg/day	40–60	190 g/day 760 kcal/day
Fats	0.75–1 g/kg/day	20–30	50 g/day 450 kcal/day

Micronutrients in the form of vitamins, minerals and trace elements should also be adequately provided to meet the needs of the patient.

- Excessive glucose is converted to fat in the liver, and produces steatosis.
- In critically ill patients, excessive use of glucose for non-protein calories nearly doubles the production of carbon dioxide. This increases pulmonary workload. Weaning therefore becomes difficult in patients on ventilator support.

Lipids

Lipids provide 30–50% of ingested calories, and are as good as hypertonic glucose in improving protein synthesis in catabolic patients. Linoleic acid is the only essential fatty acid that must be provided for. It should constitute 4% of the total caloric intake, else a fatty acid deficiency results.[12] The latter is typically seen after a few weeks of fat-free intravenous alimentation. The clinical manifestations include an eczema-like rash with neutropenia and thrombocytopenia. The syndrome can be countered by the use of intravenous lipid emulsions or the oral intake of 10–15 mL/day of safflower oil.

Protein Requirements

The minimum protein intake is 0.5 g/kg per day. In most patients in the ICU, an intake of 0.75–1 g/kg per day suffices. In highly catabolic states (severe burns, tetanus), the intake is between 1.5 g/kg per day and 2 g/kg per day.

Protein catabolism can be measured as stated earlier, by estimating the 24-hour loss of urea nitrogen in the urine. Nitrogen balance studies may help adjust protein intake. Nevertheless, it is generally impossible to prevent loss of lean muscle weight in critically ill catabolic patients. *It is therefore unwise to use large quantities of proteins.* This merely adds to the metabolic problems encountered during nutritional support. Attempts to provide adequate protein to patients in hepatic or renal failure may fail because of increasing azotemia or worsening encephalopathy. Indications for a decrease in protein administration include rising blood urea nitrogen (BUN) that exceeds 100 mg/dL or an elevated serum ammonia level that is associated with encephalopathy.

Water and Electrolytes

Carbohydrates given to a malnourished patient reduce salt and water excretion. If sodium is also provided simultaneously, there is a significant expansion of the extracellular volume, resulting in weight gain. Many catabolic states may also be associated with diminished salt and water excretion. The possibility of a fluid overload must therefore always be kept in mind following the initiation of TPN.

Vitamins

Twelve essential vitamins need to be supplied. The daily requirements may be much higher in seriously ill or catabolic patients. Low serum values of vitamins were observed in 25% of adult males in a surgical ICU.[13] Intravenous replacement therapy even in large doses failed to correct these low values in as many as 40% of these patients.[13]

Thiamine deficiency, folate deficiency and deficiency of Vitamins A, C and E are fairly often observed.[13,14]

Trace Elements

The nine necessary trace elements that need to be included in nutritional support are iron, zinc, manganese, molybdenum, copper, chromium, selenium, iodine and cobalt. They are present in many enteral feed formulations, but some of these trace elements may need to be added to TPN solutions. Requirements of trace elements may increase in patients with diarrhea or malabsorption. Supplements of manganese and copper are avoided or reduced in patients with liver cell dysfunction.

Total caloric requirement for either parenteral or enteral feeds and in particular the protein content supplied will depend both on the nature of the illness and the background nutritional state of the patient. The recommendations for nutritional requirement in different critical problems are discussed later in this chapter.

METHODS OF NUTRITIONAL SUPPORT

There are two methods of nutritional support: enteral and parenteral. Nutrition provided totally by the parenteral (i.e. intravenous) route is termed TPN. Parenteral nutrition is generally provided through a central vein; it could also be given via a peripheral vein. Both parenteral and enteral routes are often used in the same patient. Though both methods can provide equal nutritional support, the enteral mode or method is always to be preferred whenever this is possible.

The following points need to be kept in mind—

- Parenteral nutrition alters the normal physiology of nutrition. Physiological changes during parenteral nutrition include an alteration in body composition, and an increased blood flow to the gut.[15]
- Hepatic dysfunction, in particular steatosis, is frequent with parenteral nutrition. There are also changes in the blood levels of pancreatic and GI hormones.
- The absence of direct enteral stimulation by nutrients during parenteral nutrition can disturb the structural and functional integrity of the gut.[16-20]
- The absence of enteral nutrition reduces the immune function of the gut. The gut can be an important portal of entry for pathogens in critically ill patients. Translocation of bacteria from within the lumen to the mesenteric glands and then to the bloodstream is ordinarily prevented by gastric acid, intact peristalsis and normal bacterial gut flora. These factors are altered in an intensive care setting by antacids, H_2-antagonists, antibiotics, as also by disuse atrophy of the gut in patients on parenteral feeds. IgA normally present in the intestinal mucosa is also decreased in parenterally fed patients. This robs the gut of an important immune defense mechanism. It is likely that enteral feeds besides maintaining the absorptive function of the mucosa, also maintain the functional integrity of the mucosal barrier, and prevent translocation of bacteria outside the lumen of the gut. The latter aspect may be of great importance in critically ill patients in an ICU setting.
- Parenteral nutrition is far more expensive than enteral nutrition.
- Both methods can be associated with complications—technical, infectious and metabolic. Parenteral nutrition has however greater hazards when compared to enteral feeding.[21]
- Parenteral nutrition should be terminated once enteral feeds are tolerated.

ENTERAL NUTRITION

Indications

Full enteral support is indicated in the following conditions[22]—

- Malnourished patients whose oral intake is poor for 3–5 days.
- Well-nourished patients with poor oral intake for 7–10 days.
- Inability for whatever reason to eat adequately: oropharyngeal lesions, esophageal lesions, neurological disorders involving the upper GI tract.
- Following massive small bowel resection (90%)—enteral nutrition helps in the regeneration of small bowel mucosa.
- Enterocutaneous fistulae with an output of less than 500 mL/day. Enteral feeds allow absorption, and probably do not interfere with spontaneous closure of the fistulae.
- Severe full thickness burns. There is some evidence that early enteral feeds limit sepsis and reduce protein loss from the bowel in these patients.
- Following major upper GI surgery (total esophagectomy or total gastrectomy), feeds administered through a tube catheter jejunostomy are necessary.
- Following surgery for necrotizing, suppurative pancreatitis. Initial TPN in these patients is followed by jejunostomy feeds or feeds through a nasojejunal tube following recovery of small bowel function.

Although enteral feeds are generally well tolerated in critically ill individuals, there are case reports of bowel infarction during jejunal feeds in pressor-dependent patients.[23] It was postulated that jejunal feeds increased oxygen demand in a segment of the bowel that was poorly perfused. It is therefore best to commence enteral feeds only after the patient is hemodynamically stable. Initial feeds should be small; they should be gradually increased if the patient tolerates them.

Contraindications

Enteral feeds are contraindicated in—

- Generalized suppurative peritonitis.
- Complete intestinal obstruction.
- Ileus from any cause.
- Ischemia to the bowel.
- Patients with severe shock.
- Enterocutaneous fistulae with a large output.
- Acute fulminant necrotizing pancreatitis (in the early phase).

In severe uncontrolled diarrhea, we give arrowroot, electral water (water + electrolytes), weak tea without milk orally, and give the main nutritional support through intravenous alimentation.

Access

Enteral feeds can be infused into the stomach, duodenum or jejunum. This can be achieved by a nasogastric tube, nasoduodenal or nasojejunal tube, a percutaneous feeding gastrostomy, or a jejunostomy. A feeding jejunostomy is fashioned through a tube or catheter (tube jejunostomy) at surgery.

Gastric Feeding

Enteral feeds infused into the stomach can have both advantages and disadvantages. The advantage is that the stomach initiates digestion though no nutrients are absorbed. Gastric acid secretion helps to sterilize gastric contents and the risk of bacterial contamination of the gut is reduced. The stomach can also protect the gut from an osmotic load. In the presence of hyperosmotic fluid, the motility of the stomach is reduced. Gastric secretions dilute the hyperosmolar load till it is isoosmolar; the contents then pass through the pylorus into the duodenum and small gut.

The major disadvantage of enteral feeds infused into the stomach, is the development of gastric atony. Gastric atony is more frequent than atony of the small gut in critically ill patients.

Feeds cannot be continued in the presence of severe atony, else there is the danger of aspiration pneumonia. When enteral feeds are infused into the stomach, gastric residual volume should be monitored frequently—every 2–4 hours. In spite of monitoring, acute gastric atony with dilatation can occur suddenly, and in critically ill patients can cause massive aspiration of gastric contents into the lungs. It is then mandatory to discontinue gastric feeds.

Gastric feeds can be given through a nasogastric tube in critically ill patients. If for some reasons gastric feeds need to be given for several weeks or months, it is best if they are given through a percutaneous endoscopic gastrostomy (PEG).

Duodenal Feeding

Duodenal feeding is often preferred for the above reasons to gastric feeding. The feeding tube is inserted through the nostril or through a gastrostomy. At times in presence of gastric atony, it is necessary to insert a separate nasogastric tube in order to aspirate gastric contents, or to administer sucralfate for treatment or prevention of bleeds caused by stress ulcers.

The earlier feeding tubes were large bore (14–16 Fr), rigid tubes placed in the stomach. For reasons of economy, we still have to make do with these tubes. The newer feeding tubes are narrow (8 Fr), flexible and are available in longer lengths for intubation of the small bowel.[24] These tubes add to patient comfort and reduce the risk of reflux and aspiration pneumonia. Because of lack of easy availability and increased expense, we use the new narrow tubes only in rare instances. The finer tubes however have one disadvantage, and that is the risk of misplacement of the tube in the tracheobronchial tree, with disastrous consequences. The fine bore tubes require a stylet for insertion, and in ill patients with a blunted cough reflex, can quite easily go through the larynx and into the trachea. They can also pass by the side of the inflated cuff of an endotracheal or tracheostomy tube. If this goes unrecognized, a small bore feeding tube may find its way right into the pleural space. The tube position should therefore always be checked. The tip of the tube is radiopaque, and a chest X-ray should show the tube below the diaphragm. A lateral view of the chest should also be done if there is doubt about the tube placement. Aspiration of contents through the tube helps; if the aspirate has an acid content pH (<3), the tube lies within the stomach.[25]

Jejunal Feeding

Jejunal feeding is now being used frequently all over the world. It is used particularly in patients following major abdominal surgery, and severe trauma. The technique is either a needle jejunostomy or a tube (catheter) jejunostomy. A feeding jejunostomy allows full use of the gut despite ileus involving the stomach and the large bowel. When for any reason enteral feeds in the stomach are contraindicated, we prefer to infuse feeds through a jejunostomy. Technically, small bore tubes advanced through the pylorus into the small bowel, avoid quite a few problems associated with a direct feeding jejunostomy. It is often difficult to maneuver these newer fine bore tubes through the pylorus into the small bowel. The procedure is preferably done under fluoroscopic guidance.

Starting Tube Feeds

A test infusion is indicated to determine the safety of gastric feeds. A volume of N saline equivalent to the desired hourly feeding volume, is infused into the stomach (in patients with nasogastric tubes) over 1 hour. The feeding tube is clamped for 30 minutes, and the residual volume aspirated. If the volume is less than 50% of the infused quantity, gastric feeding can be started. If during feeds the aspirated residual volume increases, the feeds need to be given at a slower rate, or temporarily stopped. It is best to give the test volume as an infusion and not as a bolus. The latter causes gastric distension and can delay gastric emptying. The residual volume can then be greater than that observed if the volume load had been given by an infusion.

Feeding Patterns

Intermittent infusions are now frowned upon, though we admit to its use over the years. The popular method of delivery is by a continuous infusion over 16 hours. This is believed to reduce the risk of aspiration and diarrhea; it also produces more weight gain and a positive nitrogen balance.[26]

Tube feedings are initiated by starter regimes that use less calories and a slower infusion rate. Both caloric intake and volume are then increased to desired levels over a few days. The rationale is to initially avoid the occurrence of diarrhea by not overloading a gut, which has had no nutrients to deal with for the preceding 4–7 days. Many units however forego starter regimes, and commence full enteral feeds from the outset, except in patients who have had no enteral feeds for several days. Starter regimes should always be used when enteral feeds are administered through a jejunostomy or through a nasojejunal tube. This is because the small bowel does not have the reservoir capacity of the stomach, and diarrhea invariably results, if feeds are not initiated through starter regimes. An isotonic feeding formula is diluted to a quarter of its strength, and started at 25 mL/hour.[27] The infusion rate is increased by 25 mL every hour, till the target rate is achieved.[28] The concentration of the feeding solution is now increased over the next few days, full nutrition being achieved within 4 days.[27] Jejunal feeds are preferably given as an infusion over a 6-hour period.

Types of Enteral Feeds (Formulations)[29]

Unfortunately, very few satisfactory special formulations for enteral feeds are available in our country. A frequently used formulation is *Ensure*, which is both lactose and gluten free. 1 mL of this formulation provides one calorie. The calories contained in one serving amount to 250 calories in 250 mL. Each serving of 250 calories contains 9 g of protein (14.2% calories), 9 g of fat (31.8% calories) and 34 g carbohydrates (54% calories) + 200 g water + 24 key vitamins and minerals.

1,500 mL of the formulation (i.e six servings) would thus give a caloric intake of 1,500 calories with the distribution of protein, carbohydrate and fat as indicated above (i.e. 54 g protein, 54 g fat and 204 g carbohydrates). The formulation has an osmolarity of 379 mOsm/L H_2O.

The formulation *Ensure Plus HN* (available in Western countries) provides a higher caloric and higher protein content. Each serving contains 355 calories in 237 mL, with 14.8 g protein, 11.8 g fat and 47.3 g carbohydrates together with vitamins and minerals. This formulation is hyperosmolar (1.5 kcal/mL), the osmolarity being 500 mOsm/L H_2O.

When special formulations are available (as in Western countries), the following characteristics help in selecting the appropriate formula for the patient—

- *Caloric Density and Osmolality*—
  - The formulations that provide 1 kcal/mL are isotonic to plasma, and are preferred for small bowel feeds. They include preparations such as Osmolite or Isocal.
  - The formulations, which provide 1.5–2 kcal/mL are hypertonic or high density formulas, and are preferred when fluid intake needs to be restricted. These feeds should be administered preferably into the stomach. Gastric secretions dilute the feeds and render them isotonic before they reach the small bowel. High caloric density formulations include Osmolite HN (2 kcal/mL) and Isocal HN (2 kcal/mL).
- *Protein content* Most enteral formulas provide up to 14–20% of total calories as proteins. There is no evidence to suggest that higher protein content improves morbidity or mortality. Intact protein is more difficult to absorb than hydrolysated protein. The latter is preferred in malabsorption and in the short bowel syndrome. Peptide-based formulas can reduce diarrhea from tube feedings.[30] Formulas containing peptides and amino acids are derived from hydrolysis of casein, whey, lactalbumin and sugar.
- *Fat complexity* Median chain triglycerides are easier to absorb than long chain triglycerides, and are favored in patients with malabsorption. Most enteral formulas have long chain triglycerides, but some have a combination of both (e.g. Isocal). Linoleic acid and linoleinic acid are necessary to prevent fatty acid deficiency. Omega-3 fatty acid has been included in disease specific formulas.

Classification of Enteral Feeds[29]

Enteral feeding formulas are classified according to the nature of nutrients, or the ease of absorption.[31] The important enteral feeds and formulations available in the West are listed below.

- *Liquidized or blenderized food* They are liquid forms of table food. We can use these enteral feeds for most patients (see below).
- *Lactose-free formulas* There are several standard feeding formulas available in the West. These standard formulations are indicated in patients with a normal GI tract who do not tolerate lactose. Examples: Isocal 1 kcal/mL; Sustacal HC 1.5 kcal/mL; Isocal HCN 2 kcal/mL.
- *Chemically defined formulas* These contain hydrolysated protein instead of intact protein, to facilitate absorption, and are indicated in patients with impaired ability to absorb nutrients. Examples: Criticare HN; Vital HN.
- *Elemental formulas* The elemental formulas contain amino acids. Most of the nutrients are well absorbed in the jejunum. These are indicated in patients with limited absorptive capacity and are often used for jejunal feeds. Example: Vivonex 1 kcal/mL.

Liquefied or Blenderized Feeds

We have devised for our unit enteral feeds that contain naturally available nutrients. These nutrients include milk, whey, curds, fruit juice, protein powders, glucose, and liquidized potatoes, rice and vegetables. The protein content can be further increased in those intolerant to milk or milk products by liquidizing chicken or meat. Alternatively, high protein-containing powders can be added. The commonly used protein preparations are listed in Table 2. Fat content is provided by measured quantity of butter. This cocktail is made up to a desired volume by the addition of water and fed to the patient at the rate of 200 mL 2 hourly. It is easier to feed liquidized food in the above fashion through the old-fashioned nasogastric tube. The buttermilk diet (BMD) can be used for patients with increased caloric requirements (e.g. those with severe burns) (Box 2); 1 L of BMD provides 1,000 kcal, 60 g of proteins and 340 g of carbohydrates. Jejunostomy feeds require more meticulous preparation before they can be given through the jejunostomy catheters. Nevertheless, it is important to be aware of what is available in the outside world, even if these preparations remain at present of theoretical interest. It must be said that in our unit, the morbidity and mortality of critically ill patients given enteral nutritional support in the manner outlined above, is no higher than that observed in units in the West that use special feeding formulas. We do encounter diarrhea with the liquidized food prepared as described above, but it is generally controllable.

A sample of nasogastric tube vegetarian/nonvegetarian, blenderized feed administered in the ICU at the Breach Candy Hospital, Mumbai, is detailed in Table 3.

Complications of Enteral Feeding

- *Gastric retention, vomiting and aspiration pneumonia* These are most often observed when feeds are infused into the stomach. The reported incidence of aspiration varies from 1% to 44%.[30] Aspiration is less likely when feeds are infused into the duodenum or jejunum. A trace of bright color may be added to feeds when aspiration is suspected. If respiratory secretions aspirated through a tracheostomy or endotracheal tube are similarly colored, it is a pointer to definite aspiration.
- *Diarrhea* This is the most frequent and most troublesome complication of enteral feeding.

  The following steps should be taken to control the diarrhea—

Table 2: Commonly used protein preparations

Name of product	*Amount*	*Energy*	*Carbohydrates*	*Proteins*	*Fats*
Resource	25 g	112	15.0	4.0	4.0
Nourish standard	25 g	111	14.0	4.0	4.0
Nourish plus	25 g	128	8.0	6.0	8.0
Ensure	25 g	101	13.9	3.7	3.3
Pentasure	25 g	112	16.0	3.0	4.0
Pentasure 2.0	25 g	116	11.0	9.0	4.0
Pentasure immono max	25 g	103	13.0	6.0	3.0
Resource high protein	25 g	91	12.0	10.0	0.5
Nourish protein plus	25 g	100	12.0	10.0	1.0
Kabipro	25 g	91	10.0	11.0	1.0
Protein X	25 g	87.5	13.6	8.0	0.1
D-protein	25 g	63.5	14.0	7.0	0.5
Threptin biscuit	2 No	44	4.8	3.0	1.4
Threptin micromix	25 g	89	16.0	6.0	0.0
Albumin care	11 g	32	1.0	7.0	0.0
Nova source peptide	25 g	100	15.0	5.0	2.3
Pentasure–crit pep	25 g	123	13.0	5.0	5.6
Peptamen	25 g	116	15.0	4.6	4.5

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Box 2: Composition of the buttermilk diet

- Curd: 1 liter
- Eggs: 4
- Bananas: 4
- Sugar: 10 tablespoons
- Total volume: 1760 mL
- Calories provided: 1760 kcals
- Proteins: 60 g
- Carbohydrates: 340 g

- Reduce the feeds by half. Avoid lactose in the feeds, and avoid bolus feeding. Use Pectokab (pectin and kaolin combination), and aluminum hydroxide; stop magnesium antacids if they are being administered. Examine stools for ova, parasites and Cl. difficile toxin.
- Use isotonic and not hyperosmotic solutions.
- Check if antibiotics could possibly be causing diarrhea.
- When available, special feeding formulas containing amino acids alone, or in combination with small amounts of peptide, may be used. These may help in patients with poor digestion and absorption. In patients with pancreatitis, pancreatic enzymes need to be given with enteral feeds.
- If diarrhea still persists, tincture opium 2–3 minims thrice daily, or 10 mL paregoric twice daily may be used for 2–3 days.

Table 3: A sample nasogastric tube vegetarian/nonvegetarian blenderized feed plan

Time	*Feed*	*Quantity (mL)*
6 am	Milk (toned) + 5 tsp protein supplement	150
8 am	Oats porridge puree + 2 tsp honey	150
10 am	Veg soup + 2 tsp olive oil + potato puree	150
12 noon	Rice + dal puree + 2 tsp olive oil	150
2 pm	Sweet lime juice + 2 tsp glucose powder	150
4 pm	Soya milk + nut puree + 2 tsp honey	150
6 pm	Stewed apple puree + 2 tsp honey	150
8 pm	Chapati + chicken (or paneer) + 2 tsp olive oil	150
10 pm	Milk + 5 tsp protein supplement	150
	Water to flush the tube	150

Total quantity: 1,500 mL
Total calories supplied: 1,500 kcal
Proteins: 60 g; visible fat (olive oil): 30 mL
Protein supplement used: Pentasure powder

- If diarrhea relents slowly, build feeds to the desired levels.
- If it continues for a week, it is best to shift to partial parenteral nutrition. As far as possible, it is wise to continue with small enteral feeds (arrowroot, whey, electral water). Total stoppage of enteral feeds often

aggravates diarrhea when enteral feeding is reattempted at a future date.

- *Mechanical problems* Small bore feeding tubes become obstructed by plugs of nutrient material in 10% of patients.[32] The tube should therefore be flushed with water before and after infusion of nutrients.[33] When the tubes are not being used for infusion, they are filled with water and plugged. If the tube is blocked and the block cannot be flushed out with warm water, a warm solution of 7.5% sodium bicarbonate is used to flush the tube. If unsuccessful, the feeding tube needs to be replaced.

PARENTERAL NUTRITION[34-36]

The total caloric requirements, the protein content and the ratio of carbohydrates to fat in patients requiring TPN, have already been discussed. The indications for TPN have also been detailed earlier. The present section will briefly deal with access, type of solutions in use, methods of administration and complications.

Access

In an ICU, TPN is generally given through a central vein. Many intensivists prefer to secure the subclavian vein through the usual percutaneous technique. It is convenient for the patient who can move his head and neck freely, and allows better sterile dressings when compared to a catheter in the internal jugular vein. This central line once secured is reserved solely for infusing nutrients required for TPN. It is best not to infuse drugs, antibiotics, crystalloids or colloid infusions through this line. All other infusions are given through a separate lumen if a triple lumen catheter is in place, or through a separate peripheral vein.

Parenteral nutrition may also be infused through peripheral veins. This is appropriate for short-term nutritional support or in patients in whom central veins are inaccessible. Thrombophlebitis is frequent when peripheral veins are used because of the high osmolality of the nutrient solutions. Nutrient solutions with an osmolality greater than 900 mOsm/L invariably produce peripheral venous thrombophlebitis. Osmolality of nutrient solutions can be reduced by decreasing the glucose concentration and substituting lipid solutions to provide the necessary calories.

Types of Solutions for Use

Dextrose

Dextrose solutions (10%, 20%, 50%) supply 4 kcal/g and constitute the carbohydrate content of parenteral therapy. Solutions with an osmolarity greater than 300 mOsm/L are hyperosmolar. 500 mL of 20% dextrose solution would provide 100 g of carbohydrate with a caloric value of 400 calories.

Lipid Solutions

Fat has a caloric equivalent of 9 kcal/g. Fat emulsions in use are rendered isotonic by addition of glycerol. The chief source of fatty acids in intravenous fatty emulsions is soya bean, with or without safflower. Linoleic acid constitutes 50–65% and linolenic acid 4–9% of the fatty acid content. Fatty emulsions marketed as intralipid are available in India as either 10% or 20% fat emulsions.

Crystalline Amino Acids

The formulations available contain 40–50% of essential amino acids, and 50–60% of nonessential amino acids. Available concentrations of amino acids vary from 3.5–10%, with varying total nitrogenous content (5.4–16 g) of the solutions. The protein content is computed by multiplying the nitrogen content in grams by 6.2, so that a nitrogen content of say 10 g would be equal to a protein content of about 60 g. The exact amino acid and electrolyte profile may also vary in different formulations. From the clinical point of view all products are by and large similar. There are also solutions designed specifically for certain disorders. Solutions preferred for renal failure supply concentrated essential amino acids and L-histidine. Those preferred for hepatic encephalopathy contain a high concentration of branched-chain amino acids (valine, leucine and isoleucine). Vitamins, electrolytes, and trace elements should be provided as additives. Vitamins B and C are extremely important, as are B_{12}, folate, vitamin A and vitamin D. Most vitamins are present in formulations of amino acid mixtures. In large wounds and after major surgeries, extra vitamin C to the extent of 1–2 g/day should be given. Large doses of vitamin A and vitamin D can cause toxicity. 5,000 units of vitamin A and 500 units of vitamin D on a weekly basis are generally adequate. Trace elements, in particular zinc, need to be given separately as deficiency in these elements may result. It is important that other than sodium, potassium and chloride, calcium, magnesium and phosphates need also to be replaced, and at times replenished in depleted body stores.

Administration

Dextrose, intralipid (lipid solution), amino acid solutions can be given as separate solutions through a triple lumen catheter inserted into a central vesdin. The advantage of this method is that one can tailor the exact quantity of carbohydrate, fats, proteins and the total calories that need to be given to a critically ill patient. Currently, many manufacturers supply either all-in-one solutions or two-in-one solutions. All-in-one solutions contain dextrose, amino acid solution and lipid all-in-one pack so that all three are infused from one bag through a single lumen of a central vein catheter. An example of an all-in-one solution is Vitrimix. 1,000 mL of Vitrimix provides for 1,000 kcal; dextrose (75 g) and lipids (20% in 250 mL) supply nonprotein energy, equivalent to about 800 kcal and the nitrogen content of the solution is 7 g (roughly equivalent to $7 \times 6.2 = 43$ g protein). The osmolarity of this all-in-one solution is 960 mOsm/L.

A two-in-one solution has dextrose and an amino acid solution in one pack; the fats would need to be infused (an

Table 4: Frequently used parenteral nutrition solutions

Products	*Total energy (kcal)*	*Nonprotein energy (kcal)*	*Dextrose*	*Nitrogen*	*Lipids*	*Osmolality (mOsm/L)*
All-in-one solution						
Vitrimix (Central TPN—1000 mL)	1000	800	75	7.0	20% 250 mL	960
Celemix G* (Peripheral TPN—1000 mL)	1040	800	75	9.6	20% 250 mL	675
Kabiven (3-in-1 bag—1026 mL)	900	800	100	5.4	Soybean oil 40 g	1060
Two-in-one solutions						
Aminomix	1000	800	200	8.2	Nil	
PNA 10** (Central TPN solution 1000 mL)	1200	1000	250	8.0	Nil	1908
Nutriflex Lipid solutions	790	600	150	7.0	Soybean oil—25 g	1400
Intralipid 10%*** (250 mL)	250				Soybean oil—25 g	300
Protein solutions						
Aminoven 10%	2200	1300	–	16.0	75	1800
Celemin 10%*****	400	–	–	16.0	–	1040

*Celemix containing sorbitol as carbohydrate is also available.
**PNA 7, PNA 8, PNA 12 and PNA 16 are also available.
***Intralipid 20% and intralipid 30% are also available. Also available as 500 mL.
****Celepid 20% is also available. Also available as 500 mL.
*****Celemin 5% is also available.

intralipid infusion) separately through a separate lumen of multilumen catheter.

Parenteral nutrition may also be infused through a peripheral vein.

Table 4 lists the frequently used "all-in-one" and "two-in-one" parenteral solutions, the kcal each supplies and the contents in relation to carbohydrate (dextrose), nitrogen and fat. It also lists intralipid solutions and amino acid solutions available as separate infusions.

Monitoring the Patient

The frequency of monitoring depends on the stability of the patient's condition. Vital signs need the usual frequent monitoring. At the start of TPN a full biochemical profile, as also a full blood count, and platelet count should be done. A biochemical profile should include blood glucose, serum electrolytes, bicarbonate, blood nonprotein nitrogen (NPN), creatinine, full liver function tests, and serum proteins, with special reference to serum albumin levels. Serum calcium, phosphorus, alkaline phosphatase, pH of arterial blood and arterial blood gases should also be done. When possible, a nutrition screen should include serum levels of transferrin, prealbumin, and retinol-binding protein. These tests may be repeated once or twice weekly. Serum electrolytes and tests for liver and renal function may need to be repeated more often, depending on the patient's clinical state. The adequacy of the nutritional regime should be assessed at weekly intervals. Nitrogen balance studies may be necessary in highly catabolic complicated cases.

Complications of Parenteral Nutrition (Box 3)

Complications fall into three groups-metabolic complications, catheter-related infections, and complications related to technical problems.

Metabolic Complications

These include disorders in glucose metabolism, chiefly hyperglycemia, deficiency states and hepatic dysfunction. Deficiency states include in particular deficits of magnesium and phosphorus. Fluid and electrolyte disturbances are also observed, and are partly related to the background disease in the patient.

Hyperglycemia[37] Hyperglycemia constitutes the most frequent metabolic complication. It is often produced when 50% dextrose infusions are used instead of 20% dextrose infusions, so as to provide calories and reduce total fluid intake. Diabetics critically ill with catabolic problems show hyperglycemia in spite of large doses of insulin. Corticosteroids also enhance the hyperglycemic state. Careful monitoring of blood glucose is mandatory and an insulin infusion is best started separately through a peripheral line, the dose being adjusted to keep

Box 3: Complications of parenteral nutrition

- Metabolic complications—
  - Hyperglycemia
  - Hypoglycemia
  - Hypomagnesemia
  - Hypophosphatemia
  - Hepatic dysfunction
- Catheter-related infections—
  - Catheter-related sepsis
  - Thrombosis of the subclavian vein
- Technical complications—
  - Related to placement of the central venous catheter (see Section Procedures and Monitoring in the Intensive Care Unit)

the blood glucose levels around 150 mg/dL. Insulin, besides controlling the blood sugar, also has a beneficial effect on nitrogen balance. Large doses of insulin however may cause severe hypokalemia. Potassium replacement is therefore important.

The appearance of hyperglycemia in a previously stable patient often heralds the onset of sepsis. The latter may be clinically evident within 12–24 hours. The source of sepsis should be promptly identified and treated; the hyperglycemic state is then easily controlled.

Uncontrolled increasing hyperglycemia from one or more causes listed above, can lead to hyperosmolar nonketotic coma.[37] Fever, obtundation, focal neurological signs, seizures and death characterize the untreated syndrome. Mental obtundation without acidosis should always suggest the possibility of a hyperosmolar nonketotic state. The blood sugar levels may vary from 450 mg/dL to 1,000 mg/dL.

Therapy consists of stopping dextrose infusions, administering large quantities of insulin intravenously in an infusion, and using half-strength saline infusions intravenously.

Hypoglycemia Invariably occurs if high concentrations of dextrose infusions are suddenly stopped. Parenteral infusions of dextrose should always be slowly tapered, and never suddenly stopped. Five per cent dextrose can be infused through a peripheral vein if necessary.

Hypomagnesemia May clinically manifest with tingling in the limbs and around the mouth. Serum magnesium levels are often reduced to less than 0.6 mg/dL. The average requirement of magnesium is 8–16 mEq/day. In patients whose magnesium stores need to be repleted, or in those with diarrhea or hepatic dysfunction, the requirement of magnesium may be significantly increased.

Hypophosphatemia Inadequate intravenous administration of phosphate may progress over a period of time to increasing phosphate deficiency. Severe deficiency leads to mental obtundation and coma. Lethargy and a slurred thick speech are early features. If unrecognized, the patient becomes increasingly obtunded and fully comatose. Hemolysis, rhabdomyolysis and heart failure may occur. The normal phosphate requirement is estimated to be 90 mEq/day. This level may be increased in hypercatabolic states, or when there is excessive loss of phosphates from body stores.

Hepatic dysfunction A rise in the serum transaminases and the alkaline phosphatase is often observed in patients on TPN. It is usually a self-limited, nonprogressive complication. A progressive rise in the serum bilirubin is almost always not due to TPN. An ultrasound examination is necessary in such patients to exclude abdominal sepsis, biliary obstruction, acalculous cholecystitis or liver steatosis. The current use of glucose plus lipid solutions to share in the caloric requirement has reduced the incidence of liver steatosis. Causes that could probably contribute to hepatic dysfunction during TPN include the effects produced by breakdown products of amino acids and bacterial endotoxins, excessive carbohydrate administration, essential fatty acid deficiency, lack of enteral stimulation of the gut with altered levels of gut hormones,[1] and the presence of complicating sepsis.

Catheter-Related Infections

Catheter-Related Sepsis This is a dreaded complication of TPN. Infection can be bacterial, fungal or both. Aseptic care of the catheter, and restriction of use of the catheter solely for the purpose of TPN, has reduced the incidence of catheter-related sepsis from 6% to 27%, to the current acceptable rate of 1–3%.[1] The subject is discussed at length in the Section Fever and Acute Infections in a Critical Care Setting.

Thrombosis of the Subclavian Vein The incidence of clinically apparent thrombosis is 2–5%. Venographic studies have however shown an incidence as high as 20–50%, the majority being asymptomatic.[38] Catheter insertion may injure the intima of the vein and initiate thrombosis. A fibrin sleeve often forms around the tip of the catheter, extending for a centimeter or two proximally. This may constitute a nidus for a sleeve thrombus. Hypertonic infusions (particularly the use of 50% dextrose) are irritant and may also contribute to thrombus formation. The composition of the catheter has been incriminated in thrombosis of the subclavian vein. Polyvinyl catheters act as a strong irritant; silastic catheters have the least irritant effect. Finally, background diseases like sepsis or malignancy can lead to hypercoagulable states that promote thrombus formation.

Pain and swelling of the arm are clinical manifestations of subclavian vein thrombosis. The latter, as stated above, may however be asymptomatic. A subclavian vein thrombus may become infected, and cause a septic thrombophlebitis of the vein. Pulmonary embolization can also result.

Treatment involves prompt removal of the catheter, and anticoagulation with heparin. Treatment of septic thrombophlebitis involves in addition, the use of antibiotics.

Technical Complications

These have been discussed in the Section Procedures and Monitoring in the Intensive Care Unit. They are related to the

Table 5: Recommendations for specific clinical conditions

Clinical condition	*Initial caloric requirement (kcal/day)*	*Proteins (g/kg/day)*	*Comments*
Polytrauma	25–30	1.5	Immune-modulating formula may be of benefit
Major cardiothoracic surgery	25	1.2–1.5	Immune-modulating formula may be of benefit
Severe burns	30–35	1.5–2.5	Higher protein intake improves outcome
Fulminant tetanus	30–35	1.5–2	Higher calories and high protein intake helps blunt or reduce catabolism
Acute renal failure (not on dialysis)	25	0.5	Restrict water, sodium and potassium
Acute renal failure (on dialysis)	25	1.5	Protein needs higher because of catabolic state and loss of protein in dialysis
Liver failure	25	0.5–1	Use 0.5 g/kg/day in hepatic encephalopathy; branch chain amino acids may improve central nervous system function
Acute hypercapnic respiratory failure	25	1.2	Reduce carbohydrates to reduce VCO_2 in severe obstructive lung disease; reduce fats in TPN in ARDS
Pancreatitis	25	1–1.5	Small bowel feeds (preferably with a peptide-based formula) are well tolerated
Inflammatory bowel disease	25	1–1.5	Small bowel feeds (preferably with a peptide-based formula) are well tolerated

placement of the central venous catheter in the subclavian or jugular vein, by the percutaneous technique.

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NUTRITIONAL SUPPORT IN SPECIAL CONDITIONS (TABLE 5)

Renal Failure

Nutritional support in renal failure increases the risk of fluid overload, and uremic symptoms. The following special points merit consideration—

- Nutritional support is absolutely necessary in hypercatabolic patients with renal failure. It should be begun early and should be combined with hemodialysis or hemofiltration. If the patient is hemodynamically unstable, continuous hemofiltration is used to control fluid overload and uremia.
- In patients who are not dialyzed and are in renal failure. The protein intake is restricted to 0.5 g/kg per day, and standard formulations are used. The fluid is restricted to 0.8–1 L/day if the urine output is low. In the absence of clinical improvement, hemodialysis or hemofiltration should be commenced. Once dialysis is begun, the protein intake is suitably increased to 1 g/kg per day, or even more in catabolic states.
- If enteral feeding is used, the fluid intake and protein intake should be carefully calculated. A carbohydrate:fat ratio of 60:40 should be used to meet caloric needs. Insulin may be required to manage glucose intolerance in these patients.
- During hemodialysis, there is a loss of 6–12 g of amino acids per treatment, and a loss of 25–30 g of glucose during a 6 hour dialysis session. Hemofiltration results in the loss of 4 g amino acids per day. When calculating nutritional requirements, these losses should be considered and made good. When dialysis is in the form of peritoneal dialysis, there is a net gain in glucose of 120–150 g/day from the dialysate fluid. This amount thus needs to be subtracted from the nutritional supplementation.
- The use of essential amino acid formulas is controversial. The rationale for the use of essential amino acids is that endogenous nitrogen can be used to synthesize nonessential amino acids, thereby reducing the degree of rise in the BUN. Essential amino acid formulations are probably only indicated when a patient in renal failure is a poor risk for dialysis, and when standard formulations produce a rapid rise in the BUN. Fluid overload remains a problem even with special amino acid formulations. In less catabolic patients, the protein intake should be kept at 0.3 g/kg per day.

Hepatic Failure

If there is no encephalopathy, the protein intake is kept at 1 g/kg per day. In the presence of encephalopathy, the protein is restricted to 0.3 g/kg per day or even less, of the standard formulations and solutions. It has been shown that the infusion of branched-chain enriched amino acids improves encephalopathy in many patients. A meta-analysis of six large studies in patients with liver disease showed that the mortality in those receiving branched-chain enriched amino acids was 24% in contrast to 43% in the control group.[39] The intake of branched-chain amino acids should start with 0.25–0.5 g/kg per day. In hypercatabolic states, this is gradually increased to 1 g/kg per day. The caloric requirement should be given by glucose and fat in the ratio of 60:40.

Respiratory Failure

Nutritional support is of importance in critically ill patients with respiratory failure. The aim is to improve respiratory muscle strength to help counter the impedance to ventilation

produced by either severe restrictive disease as in acute respiratory distress syndrome (ARDS), or by severe airways obstruction as in chronic bronchitis, emphysema. A poor nutritional state is an important cause of unsuccessful weaning from ventilator support.

Patients with chronic airways obstruction who are hypercapnic may experience a further rise in PCO_2 if carbohydrates are given in excess. This is because the metabolism of carbohydrates leads to CO_2 production. A significant increase in the volume of CO_2 produced can only be got rid off by an increase in alveolar ventilation. Patients with severe chronic airways obstruction may be unable to increase their alveolar ventilation to washout the excess CO_2. The $PaCO_2$ therefore rises. Carbohydrates should be restricted in these patients, particularly when they are being weaned from ventilator support. The total caloric requirement and protein remain as described earlier but the carbohydrate:fat ratio should be 40:60.

On the other hand, in patients with ARDS, lipid emulsions may interfere with gas exchange and it is preferable to restrict fats and keep the carbohydrate: fat ratio at 65:35 when the patient is on parenteral nutrition.[40]

Cardiac Failure

The major feature in TPN is to restrict salt and water intake. Sodium, potassium and magnesium should be carefully monitored. TPN is started with half the caloric requirement over 3–4 days in order to avoid pulmonary edema secondary to refeeding and increased metabolic rate. It is then gradually increased to the required level. The caloric and protein intake is as discussed in earlier sections, with a glucose:fat ratio of 60:40. Ischemic myocardium derives its energy from anaerobic metabolism. The use of parenteral nutrition with adequate glucose, potassium and insulin may provide substrate delivery to such ischemic areas.[41]

Pancreatitis

Recent trials suggest that jejunal enteral feeds of a peptide-based diet are well tolerated in patients with severe pancreatitis. Enteral nutrition should be attempted before starting TPN in the majority of patients with acute pancreatitis. In fact, septic complications in necrotizing pancreatitis are reduced in those receiving enteral feeds when compared to those receiving TPN.[42] However, in fulminant pancreatitis with ileus and complicating sepsis, TPN is imperative. Jejunal enteral feeds should be started slowly when gut function returns.

Thermal Injury

Patients critically ill with severe burns need 30–35 kcal/kg daily and 2 g of protein per kg per day. Increased protein intake appears to reduce both morbidity and mortality in these patients. The gut should be used as far as possible; nutrition if needs be can then be supplemented by parenteral therapy.

Metabolic Stress Syndrome and Diabetes

Metabolic stress syndrome is a condition of elevated blood glucose levels in nondiabetics in an ICU setting. It is not due just to caloric intake, but is related to increase in counter-regulatory hormones and insulin resistance. It should be countered by the use of a titrated dose of insulin, so as to keep blood glucose levels not greater than 140 mg/dL. In a prospective randomized study in 765 critically ill mechanically ventilated patients, a tight control over blood glucose with insulin, reduced mortality by 43% and also resulted in a significant reduction in morbidity.[43]

Diabetic patients receiving TPN frequently have serum glucose and electrolyte levels difficult to control. Insulin administration is vital for effective parenteral alimentation. TPN should be initiated in diabetics with just 150 g of glucose in 24 hours. A quarter to half of the patients daily insulin requirement should be added to the TPN solution; further doses of subcutaneous insulin are given according to a sliding scale, the dose of insulin being based on bedside glucose estimations every 3–4 hours. It is always preferable to add insulin to the TPN solution to control elevated blood sugar levels. The use of separate intravenous infusions of insulin and TPN solution can cause severe hypoglycemia in these critically ill patients.

IMMUNONUTRITION OR IMMUNITY-ENHANCING FORMULAS

Combinations of various nutrients, which enhance immune activity and immune response have been in use over the last few years. These immunomodulating nutrients include glutamine, arginine, omega-3 fatty acids, neucleotides and antioxidant vitamins. Glutamine, which accounts for more than 60% of the body's free amino acid pool is markedly decreased in stress and starvation. Supplements of glutamine are believed to be of use in patients with multiple trauma, sepsis, severe burns, AIDS, inflammatory bowel disease. Glutamine supplements can be given by the enteral route or intravenously. Arginine plays a role in lymphocyte proliferation and wound healing. Omega-3 fatty acids may reduce production of inflammatory mediators by neutrophils, macrophages and endothelial cells. Neucleotides are believed to enhance immune function.

The use of immune-enhancing formulas are reported to be associated with lower rates of infection, decreased time on ventilator support and decreased length of stay in the ICU.[44]

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SECTION

13

Fever and Acute Infections in a Critical Care Setting

- General Considerations and Noninfective Causes of Fever in the ICU
- Nosocomial Infections
- Community-Acquired Fulminant Infections Requiring Critical Care
- Antibiotic Therapy in the Intensive Care Unit
- Invasive Fungal Infections in the ICU

CHAPTER 43

General Considerations and Noninfective Causes of Fever in the ICU

GENERAL CONSIDERATIONS

The incidence of acute infections requiring critical care is probably higher in the poor developing countries of the world than in developed regions. The nature of acute infections is also often different. In India, we see most of the infections that prevail in the West, as also other acute infections that the Western half of the world hardly ever encounters. This is related to differing geographical, environmental and socioeconomic factors.

Patients with infection in intensive care units fall into three groups—

1. *Patients with severe community-acquired infections who need critical care* These include in our part of the world, patients with bacterial sepsis, severe tetanus, severe *Plasmodium falciparum* infections, severe community-acquired pneumonia, disseminated hematogenous tuberculosis, violent Gram-negative infections chiefly originating in the gastrointestinal tract, fulminant amebic infections, fulminant meningitis, hemorrhagic dengue fever, severe leptospiral disease and other miscellaneous acute infections.
2. *Patients with nosocomial (i.e. hospital-acquired) infections* These can occur either in patients admitted to hospital wards, the infection being serious enough to merit critical care, or in patients already admitted to the intensive care unit (ICU). In our ICU, the rate of nosocomial infection in patients requiring life support for more than 2 weeks is five-fold higher than in those admitted to the general wards, who do not require ICU care. However, the proportion of nosocomial infection in the ICU vis-à-vis the general wards differs in different hospitals in Mumbai, and in different centers of this country.
3. *The immunocompromised and, in particular, the neutropenic patients in the ICU* fall in a separate category. Such patients are extremely vulnerable to nosocomial infections in the ICU, because of a hostile environment where the risk of infection is high, and also because they lack appropriate defense mechanisms against infection.

Fever and infections in neutropenic patients are dealt with in the Section The Immunocompromised Patients. Important infections and the background factors underlying these infections in the other two groups of patients are dealt with in subsequent chapters of this section. The present chapter deals with *nosocomial fever (i.e. fever that appears 24–48 hours after admission) in a critical care setting, unrelated to infection.*

FEBRILE RESPONSE

The normal temperature ranges from 36°C (am) to 38°C (pm) with a mean temperature of 37°C (98.6°F). It is measured in the mouth as oral temperature and more reliably in the rectum as the rectal temperature. A febrile response is the hallmark of infection. It is however important to bear the following facts in mind when considering the febrile response—

- Fever and its attendant symptoms of malaise, together with leukocytosis can occur in the absence of infection. A careful consideration of the background clinical features of a patient with pyrexia in the ICU, and a search for nonspecific causes of pyrexia is imperative, if unnecessary use of antibiotics (with all its attendant dangers) is to be avoided.
- The height of the fever and the clinical appearance of the patient need not constitute a reliable guide either to the presence or to the severity of the infection. High fever with

rigors could be due to a pyrogen reaction from an infusion, or due to a drug reaction, while minimal temperature elevations and even normal or subnormal temperatures may be associated with life-threatening sepsis.

- A normal oral and axillary temperature in a setting where fever is expected should always prompt one to measure the rectal temperature. A very high rectal temperature with normal or only modest elevation of axillary temperature is a feature of fulminant tetanus, in many patients with *P. falciparum* infection and in some patients with life-threatening sepsis. Rectal temperatures closely approximate the core temperature and are standard measurements in most ICUs in Europe and the United States. Oral temperature is fairly reliable (1° less than rectal and 1° greater than axillary temperature), but in problem patients, and in those with a marked discrepancy between the oral and the rectal temperatures, the latter should be monitored. Alternative methods for monitoring core temperatures are now available in the form of thermistors placed in bladder catheters, pulmonary artery catheters and ear probes. These however are expensive, and in a poor country like ours, unnecessary for patient care.
- Infants and elderly patients may not respond with the expected temperature pattern even in serious infections.

NONINFECTIVE CAUSES OF FEVER IN THE ICU[1-4] (BOX 1)

In a pyrexial patient under critical care, the clinical background or setting should dictate the initial bedside evaluation of the fever. The following noninfective causes of pyrexia should come to mind and should be carefully evaluated. Unnecessary, expensive investigations are avoided by a careful clinical examination.

TRAUMA

Trauma and, in particular, crush injuries can induce a systemic febrile response even in the absence of infection.

POSTOPERATIVE FEVER

About 10% of patients may develop an elevated temperature in the first 72 hours of surgery even in the absence of wound or other infection. Most such fevers are mild to moderate, occur as a single episode and are short-lasting. Expensive investigations are best deferred if the wound is clean and clinical examination reveals no cause for the fever. A sterile serous collection beneath a portion of the wound may lead to a low-grade fever mainly occurring in the afternoon or evenings for 8–12 days, till such time as the serous collection is absorbed or drained. Fever persisting well beyond 72 hours of surgery needs careful evaluation for possible infection. The sites needing special attention are the wound, the lungs, the urinary tract and, in patients who have had abdominal surgery, the abdomen.

Box 1: Noninfective causes of fever in the ICU

- Trauma (especially crush injuries)
- Postoperative
- Malignant hyperthermia
- Neuroleptic syndrome
- Thromboembolism
- Blood in body cavities and large hematomas
- Postcardiotomy syndrome/Dressler's syndrome
- Myocardial infarction
- Procedures or therapeutic measures, e.g. blood transfusions, infusions
- Drug fever
- Neurological causes—posterior fossa syndrome
- Pancreatitis
- Acalculous cholecystitis
- Bowel infarction
- Other rare causes, e.g. tumors, adrenal insufficiency or exacerbation of hyperthyroidism

MALIGNANT HYPERTHERMIA[5]

This is a very rare disorder caused by an abnormal release of calcium from skeletal muscles following the use of general anesthetics and muscle relaxants.[1] Initially it is characterized by muscle rigidity, tremulousness, tachycardia, labile blood pressure and ventricular arrhythmias. The striking muscle rigidity is due to the abnormal release of calcium from the sarcoplasmic reticulum of skeletal muscles.[5] Cyanosis may be marked and pulmonary embolism may be wrongly diagnosed. Fever with shivering occurs in 30% of patients; hyperpyrexia with temperatures ranging from 104°F to 107°F may occur. Fever and early features of the syndrome more often start in the operation theater during the recovery period or are apparent soon after transfer to the ICU. If untreated, myoglobinuric renal failure may be observed. Immediate treatment with dantrolene reduces morbidity and mortality. An intravenous bolus of 1–2 mg/kg of the drug is given and is repeated every 15 minutes, if necessary, to a maximum of 10 mg/kg. A maintenance dose of 1–2 mg/kg orally four times a day for 3 days is then administered.

MALIGNANT NEUROLEPTIC SYNDROME[5]

The malignant neuroleptic syndrome is a consequence of blockage of dopamine receptors from antipsychotic agents (phenothiazines butyrophenones, thioxanthenes). It is characterized by high fever, muscle rigidity, mental obtundation or delirium and excitability. There is often a marked rise in the creatine phosphokinase. It is often misdiagnosed as a central nervous system infection or a brainstem lesion. The offending drug or drugs should be stopped and dantrolene administered in the dosage stated above.

THROMBOEMBOLISM

A low-grade fever may be due to thromboembolism. This risk is highest in postoperative patients, patients immobilized for long periods of time, following cerebrovascular accidents, myocardial infarction and in patients with neoplastic disease. Careful examination for painful swelling of the calves and thighs and for tenderness over the course of the large veins in the lower limbs is at times rewarding. Even so, pulmonary emboli may be shot out from thrombi in the deep veins of the leg, thigh or from thrombosed veins within the pelvis, without the presence of abnormal physical signs.

BLOOD IN THE BODY CAVITIES AND LARGE HEMATOMAS

Accumulation of blood in the thorax, abdomen and the presence of blood in the subarachnoid space produces fever. A large hematoma in any organ or tissue occurring spontaneously as in certain diseases, or following trauma or rupture of a vessel, also produces pyrexia. A clot within a dissecting aneurysm of the aorta is similarly associated with a low-grade fever. An appropriate clinical background should suggest the correct etiology for fever in these patients.

POSTCARDIOTOMY SYNDROME/ DRESSLER'S SYNDROME

Following cardiac or open heart surgery, the persistence of a pericardial rub after 6–7 days, with fever, leukocytosis and an erythrocyte sedimentation rate more than 50 mm/hour, should suggest the diagnosis of a postcardiotomy syndrome. A pleural rub with a pleural effusion in the left pleural space or rarely bilaterally may be present. The possibility that a pleuropulmonary shadow after cardiac surgery could be due to a postcardiotomy syndrome should be kept in mind, else the diagnosis of a nosocomial pneumonia can be wrongly made.

Dressler's syndrome with fever and precordial pain due to pericarditis can occur any time from 7 days to 6 weeks after a myocardial infarct. Pleurisy and pleuropulmonary shadows may also be observed, exactly as after cardiac surgery. The response to corticosteroids is dramatic both in the postcardiotomy syndrome and in Dressler's syndrome. Response to nonsteroidal anti-inflammatory agents or to aspirin is also satisfactory in many patients.

MYOCARDIAL INFARCTION

A critically ill patient from any cause may develop a myocardial infarction. Pain in such individuals literally goes unnoticed, and a low-grade fever with leukocytosis may be cause for concern.

PROCEDURES OR THERAPEUTIC MEASURES

The following procedures or therapeutic measures are associated with fever in the absence of infection.

- *Blood transfusions or intravenous infusions of fluids* Fever is observed in about 5% of patients receiving blood products. Febrile transfusion reactions are discussed in another chapter.
- *Hemodialysis* Temporary fever during dialysis is of uncertain etiology. It could be due to noninfective causes, or due to endotoxin contamination of the dialysis equipment, or due to bacteremia by Gram-positive and/or Gram-negative organisms.
- *Fever following bronchoscopy* This occurs in 10% of patients but should not last for more than one day.

DRUG FEVER

The diagnosis of drug fever is generally made after exclusion of other causes of fever—both noninfective and infective. The fever is usually low grade, but may be high, and may be associated with chills and rigors. A drug rash and/or peripheral eosinophilia, if present, allow for an easy diagnosis; however, Mackowiak and LeMaistre[6] noted a drug rash in only 18% and peripheral eosinophilia in 22% of patients with drug fever. Tachycardia is frequent and hypotension may also occur. Contrary to conventional teaching, a patient with drug fever can appear as ill as a patient with a serious infection.[6] Any drug can theoretically speaking produce drug fever, but fever and drug reactions are most commonly observed with sulphas, quinine, quinidine, penicillin and its derivatives, antibiotics (including beta-lactams), amphotericin B, furadantin, rifampicin, phenytoin and procainamide. If drug fever is suspected, the offending drug should be omitted; if the diagnosis is correct, the fever disappears in 2–3 days.

NEUROLOGICAL CAUSES[7]

An unrecognized subarachnoid bleed is an important cause of fever. Persistent sudden headache, often accompanied by neck stiffness, is the clue.

The posterior fossa syndrome is an important cause of noninfectious origin of fever. It mimics meningitis, because of increased polymorphs in the cerebrospinal fluid (CSF), a low blood sugar and increased protein content. It is distinguished from meningitis by negative CSF culture and the gradual lessening of neurological signs as the red blood cells in the CSF clear with time.

Other causes of central fever should be kept in mind. These include trauma affecting the hypothalamus or any hypothalamic lesion. The fever is often resistant to antipyretics, exceeds 104°F and is characterized by absence of perspiration.

PANCREATITIS

This can complicate the course of a critical illness in an ICU patient, particularly with multiple organ failure, or as a complication of viral hepatitis, or following the use of corticosteroid therapy, or in the presence of shock and hypoperfusion from any cause, or in burns with sepsis.

The diagnosis may be missed in very ill patients and should be suspected if abnormal abdominal symptoms or signs, fever, or an unexplained worsening in the clinical picture is observed against a background where pancreatitis may be a possible complication. The serum amylase and lipase levels are markedly elevated, and the diagnosis can be further confirmed by an ultrasound or computed tomography of the abdomen that show an enlarged, often necrotic pancreas with pancreatic and peripancreatic inflammation (see Chapter Acute Pancreatitis).

ACALCULOUS CHOLECYSTITIS[8]

Acalculous cholecystitis is an important but often undiagnosed cause of fever. It can occur in patients with shock from any cause and is then related to poor intra-abdominal perfusion. It is also observed in patients with sepsis, in particular, abdominal sepsis. The symptoms in critically ill patients are unremarkable. Abdominal tenderness in the right hypochondrium should draw suspicion. The ultrasonography shows increased thickness of the gallbladder wall, gallbladder distension, intramural lucencies, pericholecystic fluid and intraluminal sludge. High resolution computed tomography (HRCT) of the abdomen is generally diagnostic. The diagnosis is often delayed, the disease progressing to increasing ischemia, gangrene and perforation. Surgery is mandatory.

BOWEL INFARCTION

Ischemia and/or infarction of the bowel due to occluded mesenteric vessels can produce fever and is accompanied by abdominal pain and tenderness, but these symptoms may be masked in patients who are critically ill or in those with an altered mental state. Fresh blood per rectum or melena with normal upper gastrointestinal endoscopy findings should suggest the diagnosis. HRCT of the abdomen and mesenteric angiography should prove the diagnosis.

OTHER RARE NONINFECTIVE CAUSES

Other, less common, noninfective causes of fever encountered in an ICU setting include alcohol withdrawal, severe adrenal insufficiency precipitated by the stress of a critical illness, exacerbation of hyperthyroidism in a critically ill individual, fat embolism after trauma and multiple organ failure due to a noninfective etiology. Tumors and lymphomas can also produce fever, particularly during chemotherapy. Vasculitis of any etiology is another rare cause of fever in critically ill patients.

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CHAPTER 44

Nosocomial Infections

GENERAL CONSIDERATIONS AND EPIDEMIOLOGY

Nosocomial infections are those which manifest in patients 48 hours after admission to hospital. They are therefore hospital-acquired infections, in contrast to community-acquired infections. Nosocomial infections are directly related to diagnostic, interventional or therapeutic procedures a patient undergoes in hospital, and are also influenced by the bacteriological flora prevailing within a particular unit or hospital. Infections in patients occurring within 48 hours of discharge from hospital are also invariably nosocomial in origin. Nosocomial infections carry a significant morbidity and mortality, particularly when they affect patients in the intensive care unit (ICU).

Critical care units increasingly use high technology medicine for patient care—hemodynamic monitoring, ventilator support, hemodialysis, parenteral nutrition, and a large battery of powerful drugs, particularly antibiotics to counter infection. It is indeed a paradox that the use of high technology medicine has brought in its wake the dangerous and all too frequent complication of nosocomial infections.

By a strange quirk of circumstance, the better equipped an ICU for invasive procedures, the more frequently are these procedures performed for patient care, and the greater is the risk of nosocomial infections. Prospective studies[1] have shown that various invasive devices play a far more important role in determining susceptibility to nosocomial infection than underlying disease. Again, though the concept of caring for critically ill patients in special units equipped to do so is sound, the disadvantages of such a milieu are also being increasingly realized.

The ICU milieu is uniquely conducive to nosocomial infections. It is a closed milieu, constantly full of patients with life-threatening illnesses. It has a constant staff of nurses and doctors who over prolonged periods of time are exposed to and are in contact with an environment contaminated by antibiotic-resistant pathogens. In this closed milieu the major reservoir of nosocomial organisms is the infected or colonized patient. Most bacteria, many viruses, and possibly even fungi are spread primarily via the hands of the medical, paramedical and nursing staff. Mycobacteria, Legionella and, in granulocytopenic patients, *Aspergillus spp.* are transmitted by airborne droplets. Aspiration of infected pharyngeal and mouth secretions, exposure to invasive devices and procedures, surgery, impairment of immune mechanisms or overwhelming illnesses amplify colonization and vulnerability to nosocomial infections, and promote their easy transmission. In most patients, antibiotic use promotes sooner or later antibiotic resistance to a number of organisms that prevail in a particular ICU. These resistant organisms contaminate the whole closed environment of the ICU; they can contaminate the curtains, the walls, floor and ceilings, the side tables, the wash basins and the soap dishes, the detergents used as antiseptics, and the clothing and hands of the ICU staff. Bacteria from colonized or infected patients can also be perpetuated in urine bottles, bedpans, commodes, respiratory therapy equipment, ventilators, chamber domes of transducers used in hemodynamic monitoring, and in bronchoscopes or other endoscopes.

In short, the closed milieu of the ICU provides an environment that is as conducive to the growth and preservation of resistant organisms as is a hothouse conducive to the growth and preservation of exotic flora. It is therefore not surprising

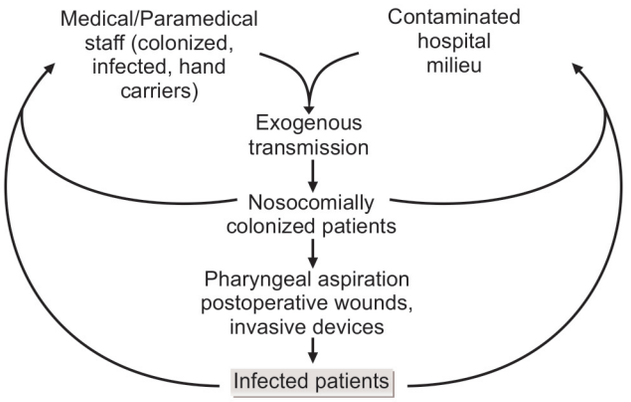


Fig. 1: Epidemiology of nosocomial infection

that two-thirds of reported outbreaks of nosocomial infections have occurred in ICUs, even though less than 10% of all hospitalized patients require ICU care.[2]

The epidemiology of nosocomial infection is illustrated in Figure 1.

INCIDENCE

The more ill the patient, the greater is the incidence of nosocomial infections. The rate of nosocomial infections is highest in burn units, surgical ICUs and ICUs for low birth weight neonates (15–30%). The risk is intermediate in medical and pediatric ICUs (5–10%), and lowest in coronary care units (1–2%).[2]

The risk of nosocomial infections in the ICU is also markedly influenced by the length of stay; the latter varies in different institutions. The Center for Disease Control and Prevention (CDC) has therefore advocated the use of nosocomial infection rates expressed per 1,000 patient days, to enable comparison between different institutions. Again, increasing exposure to invasive devices increases the nosocomial infection rate. The CDC has therefore advocated that device-associated nosocomial infections should be expressed as infections per 1,000 device days.[3-5]

The impact of nosocomial infection on mortality and morbidity in India is unknown but is unquestionably high. Nosocomial infections have been ascribed by the National Nosocomial Infection Surveillance System to be responsible for more than 80,000 deaths annually and in the mid-nineties resulted in 5 billion dollars in excess healthcare costs.[6]

Profile of Nosocomial Infections

Urinary tract infections (UTIs) are the most frequent, accounting for more than 40% of all nosocomial infections. Other nosocomial infections include nosocomial pneumonias, postoperative surgical wound infections, nosocomial bacteremias, gastrointestinal (GI) infections, especially Pseudomembranous colitis due to *Clostridium difficile*.[3]

Different ICUs have different frequency profiles of nosocomial infections. Nosocomial infections and the frequency with which they are observed in the ICU at Breach Candy Hospital, over the last 1 year have been tabled in Table 1.

Table 1: Profile of organisms isolated from patients in the ICUs at the Breach Candy Hospital, 2012

Site	*Common pathogens*
Blood	Klebsiella pneumoniae, Non-albicans Candida, Burkholderia cepacia, Pseudomonas aeruginosa and Acinetobacter baumannii complex
Lower respiratory tract	Acinetobacter baumannii complex, Pseudomonas aeruginosa, Klebsiella pneumoniae and Escherichia coli
Surgical wounds	E. coli, Pseudomonas, Acinetobacter, S. epidermidis, MRSA, MSSA
Urinary tract	E. coli, Pseudomonas, Enterococcus species, Klebsiella pneumoniae and Candida species

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

Our overall incidence of nosocomial infection over the past 1 year has been 27 episodes. The total number of ICU patients were 679; total patient days—3,823; nosocomial infection per 1,000 patient days was 3.85. Bloodstream infection (BSI) was found to be the most common form with an incidence of 17 episodes, followed by pneumonia with 7 episodes and UTI were only 3 (Fig. 2). Till 1996, UTIs headed our list of nosocomial infections, as in most ICUs all over the world. However, in the last 3 years, there has been a dramatic fall in UTIs due to continuous and active surveillance measures taken by the hospital staff.

Organisms Involved

The majority of nosocomial ICU infections are caused by Gram-negative bacilli, chiefly the Enterobactericaeae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* complex. Here again the nature and frequency of the Gram-negative organisms varies with different units. Five to ten per cent of nosocomial infections are caused by Gram-positive cocci. Most frequently the *Staphylococcus aureus* or coagulase-negative *Staphylococci* or *Enterococci*.[7] We have been fortunate in having only a small number of infections due to the *S. aureus*. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection for some reason is very uncommon in the unit, compared to the havoc MRSA has wrought in many ICUs and hospitals in the West. Close to 10–15% of infections are due to the *Candida* species. *Aspergillus spp*. and Zygomycetes infection are occasionally reported from units caring for patients with hematological malignancies, or in organ transplant patients.[8,9]

The microbiology of nosocomial infections observed in our unit at the Breach Candy Hospital is given in Figure 3.

Distinguishing between Colonization and Infection

It is extremely important that doctors in the ICU treat patients and not laboratory reports. Thus, a urine culture, or a wound

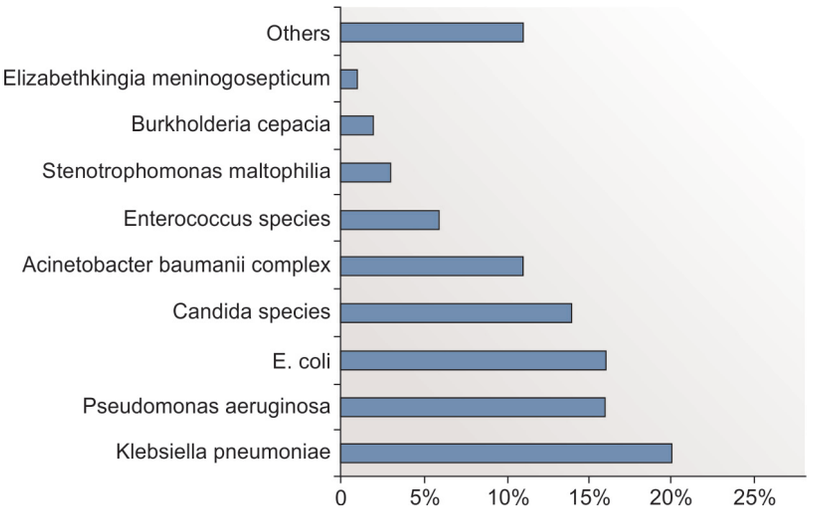
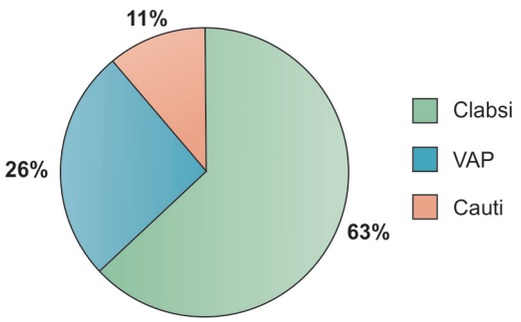


Fig. 2: Profile of organisms causing intensive care unit (ICU) nosocomial infections at Breach Candy Hospital in 2012



Clabsi—Central line associated blood stream infection
VAP—Ventilator associated pneumonia
Cauti—Catheter associated urinary tract infection

Fig. 3: Percentage (%) distribution of nosocomial infection, 2012

culture, or a sputum culture may show growth of pathogens which may merely represent colonization of the urinary tract or catheter, or of the wound or of the trachea respectively. A close liaison with the microbiology department is essential if correct interpretation of reports is to be made. Culture reports should always be correlated with clinical findings. At times, however, it may be extremely difficult to determine whether a growth of pathogens in an individual patient represents true infection or represents colonization. In many cases, particularly in the ICU, colonization is the precursor of infection, particularly in critically ill individuals, or if the organism is virulent, or resistant to antibiotics, or if the patient has invasive devices which increase his or her vulnerability.[10]

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NOSOCOMIAL PNEUMONIA

GENERAL CONSIDERATIONS

Definitions

Nosocomial pneumonia is a pneumonia that develops in patients admitted to the hospital for more than 48 hours.[1] It is a dreaded complication which chiefly afflicts the most critically ill patients in a hospital.

Ventilator-associated pneumonia (VAP) is a pneumonia that develops in a tracheally intubated patient who has been mechanically ventilated for at least 48 hours.

Healthcare-associated pneumonia (HCAP) is a new entity that has been defined by the American Thoracic Society (ATS)[1] for the diagnosis and treatment of nosocomial pneumonia. Risk factors for developing HCAP are residence in a nursing home or extended care facility, hospitalization for 2 days or more within the preceding 90 days, home infusion or antibiotic therapy, chronic dialysis within 30 days, home wound care, and a family member with multidrug resistant (MDR) pathogen colonization or infection. Though these patients are not in hospital, the above stated risk factors predispose to colonization by pathogens present within hospitals including colonization by MDR organisms.

There is some controversy over the etiology of HCAP between American and European data. While American studies report HCAP being caused chiefly by multi-resistant organisms, European data report greater similarities between HCAP and community-acquired pneumonia rather than with hospital-acquired pneumonia.

This chapter chiefly focuses on VAP—undoubtedly the commonest cause of nosocomial pneumonia.

Neiderman and coworkers[2] observed that in an intubated population treated in a surgical ICU, pneumonia developed approximately in 10%, whereas in a medical ICU, 20% of intubated patients developed this complication. Impairment of defense mechanisms of critical ill patients and easy access of dangerous pathogens to the lower respiratory tract are both equally responsible factors. The ICU milieu is therefore an ideal setting for this major complication.

The true incidence of nosocomial pneumonia is difficult to determine, chiefly because of the difficulty in reaching a precise diagnosis, particularly in patients who already have significant radiological shadowing within the lung to start with, as, for example, in patients with acute lung injury and acute respiratory distress syndrome (ARDS).

Cook et al.[3] reported that the risk of VAP is 1% per day on mechanical ventilation. The risk changes over time, being 3% for the first 5 days on mechanical ventilation, 2% from the 5th to the 10th day and 1% for the remaining days. They noted that nearly half of VAP cases occurred during the first 5 days of mechanical ventilation.

Sopena and colleagues[4] reporting in 2005 on a Spanish study on the epidemiology of nosocomial pneumonia in non-ICU patients noted that nosocomial pneumonia was observed chiefly in elderly patients with underlying disease. The mortality rate was 26% and the risk of VAP 1% per day.

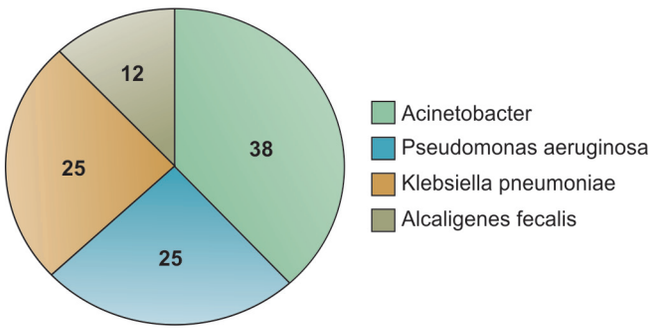


Fig. 4: Percentage (%) distribution of pathogens causing ventilator-associated pneumonia (VAP) in 2012 at the Breach Candy Hospital

Pertinent Data on VAP[5,6]

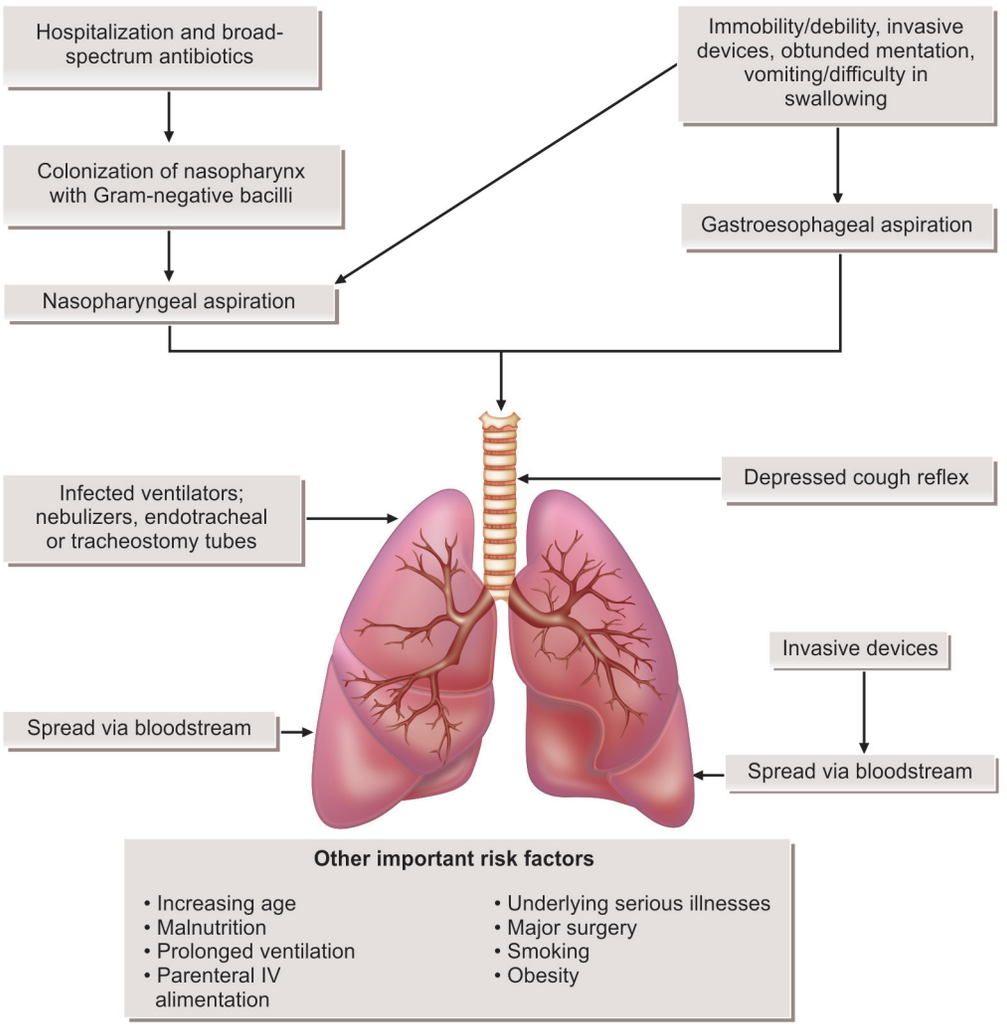
- Ventilator-associated pneumonias are the second most common nosocomial infection in many ICUs often constituting one-third or more of total nosocomial infections.[5]
- Over 90% of ICU acquired nosocomial pneumonias occur during mechanical ventilation and 50% occur in the first 4 days of ventilation.
- Early onset VAPs (<5 days of hospitalization) usually carry a better prognosis and are often caused by antibiotic sensitive bacteria. Late onset VAP (>5 days) are more likely to be caused by MDR pathogens and are associated with increased morbidity and mortality
- Between 10–20% of patients who require ventilation for more than 48 hours will acquire VAP with a mortality of 15–50%.[6]

The incidence of nosocomial pneumonias in various ICUs in our country or for that matter in any of the large metropolitan cities is undetermined, chiefly because no one has bothered to answer this question and little or no data is available. In our unit in Mumbai, nosocomial pneumonias are nowhere as frequent as reported from ICUs in the West, being 1.2–1.3 per 1,000 ventilator days.

The incidence of VAP in an ICU depends on the age of the patient, the severity of the underlying critical illness, comorbid factors, whether the lungs were normal or not at the start of mechanical ventilatory support, and the respiratory and overall critical care offered by a unit. In fact these are also the very factors that influence mortality. The length of ventilator support also influences the mortality; yet younger patients with normal lungs to start with can be maintained for weeks and even months without the course of the illness being complicated by VAP.

The microbial profile at the Breach Candy Hospital for VAP in the year 2012 is illustrated in Figure 4.

Flowchart 1: Pathogenesis of nosocomial pneumonia



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PATHOPHYSIOLOGY (FLOWCHART 1)

Aspiration

Almost always, nosocomial pneumonia is due to aspiration of infected secretions or particulate matter from the mouth and pharynx into the lower respiratory tract. Retained infected secretions within the large and small airways can also produce nosocomial pneumonia. In most sick patients in the ICU, the oropharynx is colonized by aerobic Gram-negative bacteria within 5–10 days, whereas in healthy adults the normal organisms are anaerobic bacteria, and harmless commensals like *Neisseria pharyngitidis*.

Colonization of patients can occur from exogenous and/or endogenous sources. Exogenous sources include the hands, clothing, equipment of doctors, nurses, healthcare workers and the unhealthy environment of the ICU. Other exogenous sources include colonized bronchoscopes, humidifiers, respiratory equipment, and contaminated nebulizers. Endogenous sources include pathogens contaminating and colonizing the oropharynx, the GI tract, the proximal trachea and the endotracheal or tracheostomy tube.

Tracheal intubation is the most important underlying predisposing condition for the development of pneumonia as it aids aspiration of pathogens and prevents intrinsic respiratory defenses from coming into play. The endotracheal or tracheostomy tube also can further facilitate aspiration, as pathogens often grow on the inner surface and can be aspirated or translocated into the lung. The endotracheal tube is often lined by a biofilm consisting of bacteria embedded in an exopolysaccharide matrix. Embedded bacteria are protected from both antibiotics and the host immune responses and are difficult to eradicate. During tracheal aspiration, mechanical ventilation, bronchoscopy, particles of this biofilm may be dislodged and pushed into the lung leading to lower respiratory tract infection.

The severity of the illness plays an important role in perpetuating this colonization. Invasive diagnostic and therapeutic procedures further promote the aspiration and transfer of infected, colonized oropharyngeal contents into the lower respiratory tract. The upper airway is usually colonized before the lower airway, but organisms such as *Ps. aeruginosa* can colonize the lower airway as a primary event.[7] The reason

for colonization of the mouth, oropharynx and airways by pathogenic bacteria and in particular by Gram-negative organisms, is the subject of research. In healthy individuals a film of fibronectin covers the epithelium lining the mucosa of the mouth and oropharynx, and prevents the Gram-negative bacteria from adhering to the epithelial cells. This protective coating is lost in very ill individuals, so that pathogenic Gram-negative organisms adhere to receptors present on epithelial cells of the mucosa and soon colonize it. The number of these bacterial receptors on both upper and lower airway epithelial cells is increased in many illnesses. This change is associated with increased colonization at these sites. Risk factors for increased colonization due to enhanced adherence of bacteria to mucosal cells in the airways include serious illnesses, smoking, azotemia, surgery and malnutrition.[8]

Gastric Colonization

The acid within the stomach serves as a major deterrent to bacteria swallowed in the saliva. If gastric acidity is suppressed by the use of antacids and H_2 antagonists, the bacteria within the stomach survive, multiply, and soon colonize the upper GI tract. Gastric contents laden with Gram-negative bacteria could easily regurgitate and be aspirated into the lungs, causing aspiration pneumonia. This is particularly frequent in obtunded patients, sedated patients or following a large vomit. Prophylaxis and treatment of bleeding stress ulcers with sucralfate do not significantly increase gastric pH in most patients, and results in a reduced incidence of nosocomial pneumonias.

Hematogenous Pneumonia

Rarely infected emboli from a septic thrombophlebitis can lead to septic infarcts within the lung. Catheter-related sepsis or any other source of sepsis can cause bacteremia with hematogenous spread of infection into the lungs, causing pneumonia.

Inhalation Pneumonia

Contaminated respiratory equipment (nebulizers, humidifiers, ventilator tubing, etc.) as mentioned earlier is a source of infected aerosols. Infected particles 3–5 μm in size can be deposited into the terminal bronchioles and alveoli, thereby causing a lower respiratory tract infection.

Iatrogenic Causes

Lack of aseptic precautions during suction of tracheobronchial secretions, either through an endotracheal tube or tracheostomy is an important cause of lower respiratory tract infection.

FACTORS PREDISPOSING TO NOSOCOMIAL PNEUMONIAS (BOX 1)[3,9]

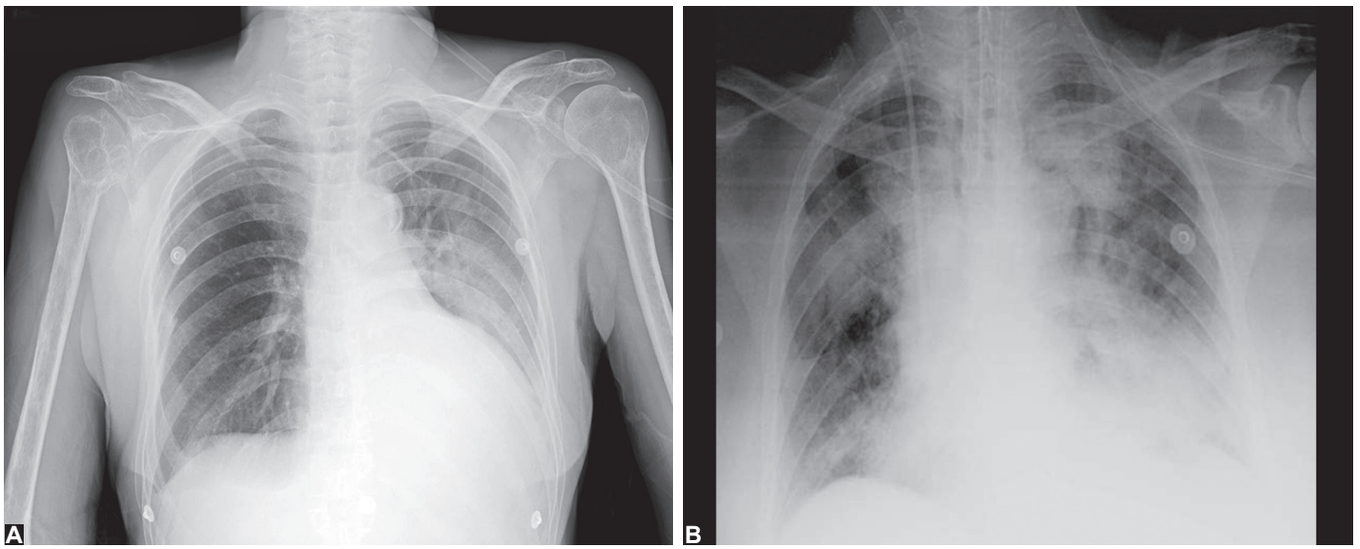
Box 1: Factors predisposing to nosocomial pneumonia (also applicable to other nosocomial infections)

- Host factors—
  - Overwhelming infections or serious illnesses, e.g. severe sepsis, prolonged shock, burns, severe trauma or following major surgery
  - Background factors, e.g. chronic lung diseases, diabetes mellitus, cardiac, renal or hepatic dysfunction, advanced age, underlying malignancy, malnutrition
  - Total parenteral nutrition
- Therapeutic interventions—
  - Endotracheal intubation or tracheostomy with mechanical ventilator support
  - Use of invasive procedures (including central lines)
  - Nasogastric tube
  - Use of corticosteroids or chemotherapy
  - Prolonged use of antibiotics
  - Colonization of upper GI tract with Gram-negative bacteria following use of antacids/H_2-antagonists
  - Use of high FiO_2 whilst on mechanical ventilation
- Environmental factors—
  - Overcrowding
  - Overall unclean environment (unfortunately so frequently seen in developing countries)
  - Transmission chiefly through contaminated hands of ICU personnel
  - Increased prevalence of multiple, resistant organisms

Abbreviations: GI, gastrointestinal; ICU, intensive care unit; FiO_2, fraction of inspired oxygen.

These can be divided into—

- *Host Factors* in which defense mechanisms are suppressed by—
  - Overwhelming infections, serious illnesses, e.g. severe sepsis, extrapulmonary infections, prolonged shock, burns or severe trauma, or following major surgery.
  - Background factors which are associated with a greater propensity to infection. These include underlying chronic lung disease (chronic bronchitis), diabetes mellitus, cardiac disease, renal failure, liver cell dysfunction, underlying malignancy, advanced age, malnutrition prior to the onset of a critical illness or occurring acutely during the course of an illness, and total parenteral nutrition.
- *Therapeutic Interventions* The most important of these are endotracheal intubation, tracheostomy, and mechanical ventilation. Nasogastric tubes encourage gastric colonization with pathogens, and perhaps provide a scaffolding or conduit for these pathogens to reach the pharynx; aspiration of these pathogens or of infected particulate matter results in pneumonia. Corticosteroids or antimitotic agents are immunosuppressants, and their use both encourage and mask infection. As mentioned earlier, there is evidence that excessive neutralization of acid to treat upper GI bleeds by antacids and H_2 antagonists also facilitates upper GI tract colonization with Gram-negative bacteria, and predisposes to pulmonary infection. The use of very high oxygen concentrations in mechanical ventilation over prolonged periods of time may also be



Figs 5A and B: (A) Unilateral nosocomial pneumonia; (B) Bilateral nosocomial pneumonia

detrimental to lung morphology and physiology, and may well predispose to infection. Prolonged antibiotic therapy can induce a superinfection by organisms resistant to conventional therapy, and lead to nosocomial pneumonia resistant to the usual antibiotics.

- *Environmental Factors* Overcrowding, an overall unclean environment (which unfortunately is frequently seen in developing countries), increased prevalence of multiple, resistant organisms, and transmission chiefly through the contaminated hands of ICU personnel, all predispose to the development of nosocomial infections.

CLINICAL DIAGNOSIS[5,10]

The clinical diagnosis of nosocomial pneumonia, including VAP, is difficult and often erroneous. This is proven by a postmortem study showing that the clinical diagnosis of pneumonia was incorrect in 60% of cases.[12] The diagnosis of nosocomial pneumonia requires the presence of the following important features—

- Fever, leukocytosis, purulent sputum or, in the case of VAP, purulent tracheal secretions. At least two of these three clinical criteria should be present.
- A chest X-ray which shows a new or progressive alveolar infiltrate (Figs 5A and B). The presence of an abnormal radiographic infiltrate together with at least two out of three clinical criteria stated above has a high degree of sensitivity but a low specificity. When all three clinical criteria are present in a patient with a fresh alveolar infiltrate on an X-ray chest, the specificity improves but the sensitivity falls to an unacceptable level (<50%).

Diagnostic problems in an individual patient can be formidable for the following reasons—

- A systemic inflammatory response characterized by fever and leukocytosis may be present, but its absence does not exclude the diagnosis of pneumonia. Also, fever and leukocytosis can occur in infections other than pneumonia and in noninfective pathologies in a critically ill patient.
- Absence of sputum or of significant lower respiratory tract secretions in patients with a tracheostomy (with or without ventilator support) does not exclude pneumonia in the presence of a recent infiltrate on an X-ray chest in critically ill patients.
- A shadow on a chest X-ray is not necessarily inflammatory. Localized shadows in one or both lung fields can be due to pulmonary edema, pulmonary hemorrhage, pulmonary infarction, ARDS and other noninflammatory causes. Atelectasis is often mistaken for pneumonia in a critically ill patient. A clearing of the shadow after vigorous physiotherapy differentiates infiltrates caused by atelectasis from those due to infection. The other causes of shadows on the X-ray chest are listed in Box 2.

Box 2: Pneumonia accounts for only one-third of pulmonary infiltrates in the ICU

- Other causes of shadows on X-ray chest—
  - Atelectasis
  - Pulmonary edema
  - Pulmonary infarction
  - Hemorrhage
  - Lung injury (ARDS)
  - Drug reaction
  - Recurrence or spread of mitotic disease
  - TRALI (Transfusion related acute lung injury)

Abbreviations: ICU, intensive care unit; ARDS, acute respiratory distress syndrome.
Source: Singh N, Falestiny MN, Rogers P, et al. Pulmonary infiltrates in the surgical ICU: prospective assessment of predictors of etiology and mortality. Chest. 1998;114(4):1129-36.

Table 2: The Clinical Pulmonary Infection Score (CPIS)

Criterion	*0*	*1*	*2*
Temperature (°C)	≥36.5 and ≤38.4	≥38.5 or ≤38.9	≥39 or ≤36
Leukocytes, mm^3	≥4000 and ≤11000	<4000 or >11000	<4000 or >11000 + immature neutrophils >50% or >500
Chest X-ray infiltrates	No	Diffuse	Localized
Tracheal secretions	Not purulent or absent	Not purulent	Abundant and purulent
PaO_2/FiO_2	>240 or ARDS		≤240, no ARDS
Microbiology	Negative		Positive

Abbreviations: ARDS, acute respiratory distress syndrome; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in blood.
Source: Pugin J, Auckentholer R, Mili N, et al. Diagnosis of ventilator associated pneumonia by bacteriologic analysis of bronchoscopic and non-bronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis. 1991;143:1121-9.

It should be remembered that a portable chest X-ray may be difficult to interpret in an intubated critically ill patient. Pneumonia may be difficult to exclude because of the technical quality of the film. Also, the chest X-ray may miss out on subtle features which are quite evident on a computed tomography (CT) of the chest.

In a study of autopsy-proven VAP, no single radiographic sign had a diagnostic accuracy greater than 68%. The presence of air bronchogram or alveolar opacities in patients without ARDS was the only sign that corresponded best with pneumonia, predicting 64% of pneumonias in this study.[11, 13]

A clinical study showed the presence of lung infection in only 42% of patients diagnosed as VAP, proving that there is a poor correlation between clinical features and bacteriological demonstration of VAP.[12]

- Nosocomial pneumonia in a patient with ARDS may be impossibly difficult to diagnose on a chest X-ray. A number of pathologies can cause asymmetric consolidation in patients with ARDS. An air bronchogram on a chest X-ray in a patient with ARDS is not necessarily predictive of nosocomial pneumonia.

Clinical Pulmonary Infection Score (CPIS) (Table 2)[13]

This scoring device is a simple aid to the diagnosis of VAP. It is based on the assessment of six clinical parameters—(1) temperature, (2) purulence of tracheal secretions, (3) total blood leukocyte count, (4) pulmonary radiological findings, (5) oxygenation and (6) semiquantitative culture of the tracheal aspirate. Each of these parameters carries 0–2 points. A value of greater than or equal to 6 was the threshold for a fairly accurate diagnosis of VAP. Studies have shown that the CPIS has a low sensitivity and specificity for diagnosing VAP. The PaO_2/FiO_2 ratio is however a valuable marker; improvement in this marker on treatment signified a better outcome, whilst a lack of response signified a worse outcome.

Newer Streamlined Surveillance Definitions and Guidelines

With the purpose of improving the efficacy and objectivity of VAP diagnosis, the Centre for Disease Control (CDC) has proposed an approach which focuses on ventilator-associated complications, centered on worsening oxygenation and systemic signs of infection.[14] Remarkably, this new approach includes an algorithm which excludes the use of chest radiography. Instead of merely considering VAP versus non VAP, the newer guidelines categorizes patients into three groups—

1. Patients with ventilator-associated complications (VAC). These patients are far more sick than those who do not have VAC.
2. Those with infection-related ventilator-associated complications.
3. Patients with probable versus possible ventilator associated pneumonia.[14] These groups represent patients at various stages in the above spectrum.

The basic features of each of these groups are summarized in Table 3.

Certain questions need to be answered with regard to these new definitions and guidelines. Do these guidelines add greater clarity on our concept of VAP? Do they help improve the management of VAP? If chest radiography is excluded would not one miss a stable VAP which does not significantly alter gas exchange?

Finally, VAC are not always due to infection and the incidence of VAC may not be reduced by measures at VAP prevention. The relation of the quality of patient care to the incidence of VAC is unproven.

We need to wait to see how necessary and useful these new guidelines are, before we set older CDC guidelines of pneumonia and VAP aside.

When considering the older CDC guidelines on nosocomial pneumonia and VAP, it is apparent from the earlier discussion that though clinical features combined with radiological findings are of help, they lack sufficient specificity in the diagnosis of nosocomial and VAP. Bacteriological evidence of pulmonary parenchymal infection is therefore also considered necessary to make a firm diagnosis. The cost-effectiveness of different methods used to obtain this bacteriological evidence and the relation of the evidence obtained to ultimate patient management and patient outcome are matters of continued discussion. These methods are briefly discussed below.

BACTERIOLOGICAL DIAGNOSIS

Noninvasive Modalities

Examination of Expectorated Sputum

Microscopic Examination

This is useful in determining the presence and at times the site of infection (upper airways, lung parenchyma).

Table 3: Newer streamlined surveillance definitions and guidelines

Ventilator associated complication (VAC)	*Any one of the following criteria*	
	Minimum daily FiO_2 increases by 0.2 over baseline and persists for >2 days	Minimum daily PEEP increases by >3 cm H_2O over baseline and persists for >2 days
Infection-related ventilator associated complication	*Includes both the features given below*	
	Temperature >38°C or	A new antibiotic started and continued >4 days
	WBC >12000 or <4000 mm^3	
Possible VAP	*After 3rd day of ventilation and within 2 days of worsening oxygenation, any one of the following criteria is met*	
	Purulent tracheobronchial secretions showing >25 neutrophils and <10 squamous epithelial cells per low power field	Positive culture of sputum/endotracheal aspirate/BAL/ lung tissue or protected specimen brushing (PSB)
Probable VAP	*After 3rd day of ventilation and within 2 days of worsening oxygenation, any one of the following criteria is met*	
	Purulent respiratory secretions from one or more specimen collections and one of the following— 1. Positive culture of endotrcheal aspirate >10^5 CFU/mL or Positive culture of BAL >10^4 CFU/mL or Positive culture of lung tissue >10^4 CFU/mL or Positive culture of PSB >10^3 CFU/mL	One of the following without the need for purulent respiratory secretions— 1.Positive pleural fluid culture (specimen obtained following thoracocentesis or initial placement of ICD only) or positive lung tissue histopathology or positive serology for common viral infections like adeno, RSV and influenza

Leukocytes

More than 25 leukocytes per low power field denote infection, but not necessarily pneumonia. Marino[15] stresses the importance of using the presence of epithelial cells of the oral cavity in a sputum sample as markers of the mouth and upper airways, while alveolar macrophages and elastin fibers are used as markers of the distal airspaces and lung parenchyma respectively. The epithelial cells of the oral cavity are large flattened cells with abundant cytoplasm, and if a sputum sample contains many such epithelial cells, it is not suitable for further examination or culture. On the other hand, alveolar macrophages inhabit only distal airspaces so that their presence denotes that at least a part of the specimen being examined is from the lower respiratory tract. The presence of elastin fibers in the sputum sample is often used as evidence in favor of a necrotizing pneumonia. These fibers are filamentous structures visualized by placing a drop of KOH over the sputum sample. When present, the elastin fibers appear as clumps of interlocking filaments and denote a destructive parenchymal lesion within the lungs.

Sputum culture

It is always necessary to screen sputum samples before doing cultures. Only samples that represent secretions from the respiratory tract (and not from the oropharynx) are suitable for culture.

Endotracheal Aspirates

The noninvasive method of obtaining respiratory secretions for culture and antibiotic sensitivity is through aspiration of endotracheal secretions with a suction catheter either through the endotracheal tube or a tracheostomy tube.

Given below are the methods by which cultures (followed by antibiotic sensitivity reports) can be processed—

1. Qualitative Culture

This is the simplest and easiest to perform and is the usual method followed in developing countries. It is however worth stressing that qualitative cultures of endotracheal aspirates in a suspected VAP may give rise to a number of false positive results (mainly Gram-negative bacilli) and may lead to the over-diagnosis of pneumonia and a misdiagnosis of its cause. Qualitative cultures of endotracheal secretions have a high sensitivity and a low specificity. In patients with pneumonia documented by histopathological examination, the endotracheal aspirate sensitivity was 82% and the specificity only 27%.

Another feature of clinical significance is that secretions aspirated from an endotracheal or a tracheostomy tube which has been in place for 5–7 days often grow Gram-negative organisms (including *P. aeruginosa*) on a qualitative culture because of colonization of the trachea by these bacteria. A positive tracheal qualitative culture therefore does not necessarily indicate infection or pneumonia nor does it necessarily indicate the organism responsible for the pneumonia, if pneumonia is indeed present. The difficulties in interpreting results of qualitative cultures of tracheal aspirates in relation to a possible VAP make one wonder as to how cost-effective these cultures are and how frequently they should be ordered in poor developing countries.

Yet qualitative cultures continue to be performed in most ICUs of poor developing countries when there is a suspicion of a nosocomial pneumonia (including VAP).

The reasons given for this persistence are listed below—

- The diagnostic test is noninvasive, cheap and requires no expertise compared to invasive testing. Even a junior nurse can perform an aspiration procedure at the bedside.

- Qualitative cultures of tracheal aspirates usually identify pathogenic organisms also found by invasive tests. They therefore have a high sensitivity. They however frequently identify nonpathogenic organisms, reducing the specificity and predictive value of the test.[16]
- Most importantly, if cultures are negative for pathogenic bacteria, VAP is very unlikely, unless the patient has received antibiotics prior to the culture test.
- As will be discussed later, a Cochrane meta-analysis suggests that there is no difference between qualitative and quantitative cultures with regard to the final outcome in VAP.

The practical management of a patient with nosocomial VAP may be influenced by tracheal aspirate (qualitative) culture sensitivity tests under the following circumstances—

- If there is an absence of response to empiric antibiotic therapy, a culture sensitivity test of the tracheal aspirate may help in the correct choice of antibiotics.
- If cultures of respiratory tract secretions grow *Staphylococci,* in a unit where this organism is uncommonly found, an appropriate antibiotic against this organism should be used, rather than the usual antibiotic combination against Gram-negative organisms.

2. Quantitative and Semiquantitative Cultures of Endotracheal Aspirates

These methods are being increasingly used to improve the specificity of endotracheal aspirate cultures.

Semiquantitative cultures are done by plating. It is technically easy and many microbiological laboratories in India use this technique.

Quantitative cultures are technically more difficult, laborious and at least in India are generally reserved for research purposes. They have no significant advantage over semiquantitative cultures.

If clinical features lend strong suspicion to the diagnosis of VAP, a culture yielding 10^6 or greater concentration of organisms on the quantitative test supports the diagnosis of nosocomial pneumonia. When quantitative cultures are performed on endotracheal aspirates, the sensitivity falls but specificity increases when compared to qualitative cultures of endotracheal secretions.[16]

Invasive Methods[5]

Role of PSB Sampling

Samples of lower respiratory tract secretions can be collected by special protected brushes through a fiberoptic bronchoscope (PSB sampling). The brush is housed in a catheter that is plugged at the distal end. The protective housing allows the catheter to be advanced through a bronchoscope without coming into contact with the upper airways. Brushings should be obtained from the area of abnormal radiological shadows observed on the X-ray chest. The material should be stained by Gram stain and cultured qualitatively and quantitatively. A culture yielding 10^3/mL or greater concentration of organisms supports the diagnosis of nosocomial pneumonia and identifies the pathogen.[17] The sensitivity for PSB tests ranges from 33% to 100%, with a median of 67%, and the specificity ranges from 50% to 100% with a median of 95%. PSB sampling therefore offers greater specificity and lesser sensitivity in the diagnosis of nosocomial pneumonia.

Bronchoscopic procedures even when performed expertly carry a risk to critically ill patients on ventilator support. The main complication is hypoxia during the procedure; this could lead to hypotension, arrhythmias and even death. Hypoxia may persist for several hours after the procedure, particularly in patients with ARDS.

Role of BAL

Bronchoscopic alveolar lavage has also been used in the diagnosis of VAP. The sensitivity of quantitative BAL fluid cultures ranges from 42% to 93% with a mean of 73%. For quantitative cultures, a CFU (colony forming units) count/mL of 10^4 is considered a positive result. The specificity ranges from 45% to 100% with a mean of 82%.

Role of Blinded Invasive Procedures

The risk and expense entailed in bronchoscopic procedures has led to the development of other tests requiring less expense, expertise and risk. These tests include the following non-bronchoscopic techniques: blinded bronchial sampling (BBS), mini-BAL, blinded sampling with PSB (BPSB). The sensitivity and specificity are reported to be similar to bronchoscopic techniques.

Positive Blood Culture, Positive Culture of a Pleural Exudate

In a patient with clinical and radiological features compatible with nosocomial pneumonia, a positive blood culture is generally a pointer to the nature of the organism causing the infection. However, a patient could develop nosocomial pneumonia, for example by aspiration of infected oropharyngeal secretions and also have a separate bloodstream infection from an intravascular device such as the central venous catheter (CVC). On the other hand, cultures of an organism from a tapped pleural exudate are certain specific bacteriological evidence of nosocomial pneumonia. Unfortunately, pleural effusions or empyemas are infrequent and blood cultures come positive only in a small minority of patients with nosocomial pneumonia.

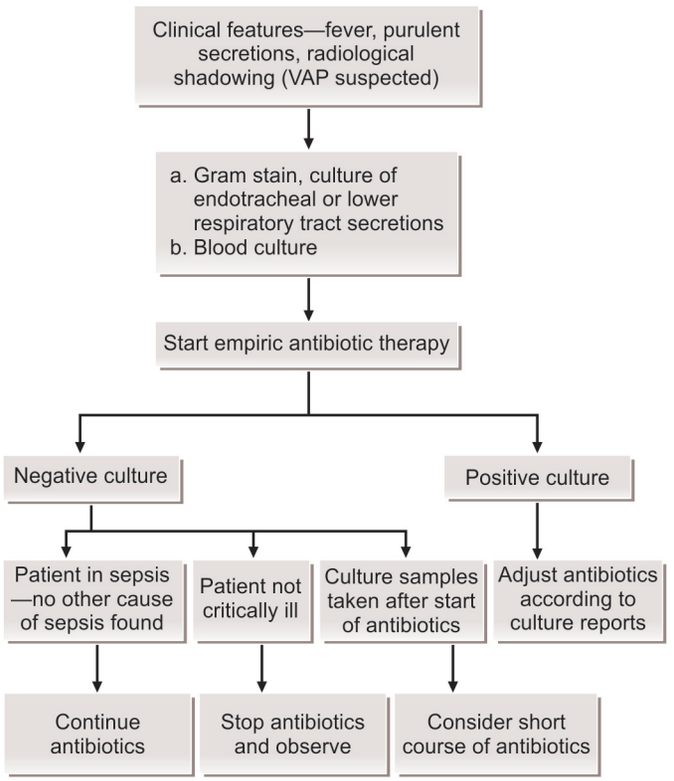
Summary of a diagnostic strategy for a hospital-acquired pneumonia (including VAP) is given in Flowchart 2.

Evaluation of Diagnostic Strategies

Are invasive strategies for culture of lower respiratory tract secretions superior to noninvasive strategies for culture of tracheobronchial secrections?

- There have been four randomized controlled trials[18-21] studying the impact of invasive versus noninvasive strategies on ultimate outcome (mortality), antibiotic

Flowchart 2: Algorithm for the clinical approach to hospital-acquired pneumonia [including ventilator-associated pneumonia (VAP)]


Clinical features—fever, purulent secretions, radiological shadowing (VAP suspected)
a. Gram stain, culture of endotracheal or lower respiratory tract secretions
b. Blood culture
Start empiric antibiotic therapy
Negative culture
Positive culture
Patient in sepsis—no other cause of sepsis found
Patient not critically ill
Culture samples taken after start of antibiotics
Adjust antibiotics according to culture reports
Continue antibiotics
Stop antibiotics and observe
Consider short course of antibiotics

use in patients with clinical suspicion of nosocomial pneumonia. There was no difference in outcome between an invasive strategy (PSB and/or BAL) versus a non-invasive strategy (quantitative endotracheal aspirate culture).

- One larger trial[21] however showed a small reduction in mortality, and morbidity using an invasive strategy (PSB or BAL), as also better sequential organ failure assessment (SOFA) scores and lesser use of antibiotics. This study however compared invasive strategy with a qualitative culture of tracheal aspirates and could not be strictly compared with the other trials.
- Most importantly, Shorr et al.[22] reported on a meta-analysis of pooled data from these randomized studies on 628 patients and observed that the invasive approach did not alter mortality. Invasive testing was however associated with improved antibiotic utilization, or offered a change of antibiotic therapy after sampling.

It is strongly recommended that cultures within the respiratory tract (either invasive or noninvasive sampling) should be sent before starting a new antibiotic or before changing a previous antibiotic regime. If this is not done false negative tests are likely to result.

It would appear from the preceding discussion that quantitative cultures of endotracheal aspirates being more specific are to be preferred to qualitative cultures. This concept though sound in theory, is not necessarily true in practice. Results of a study on qualitative versus quantitative cultures of respiratory secretions for clinical outcomes in patients with VAP are summarized below.[23]

Meta-analysis of five randomized controlled trials (RCTs) with 1,367 patients revealed the following—

- Quantitative cultures did not score over qualitative cultures to reduce mortality among patients with VAP.
- There was no evidence to show that the use of quantitative cultures resulted in a higher rate of antibiotic change, reduction in ICU stay, reduced time on ventilator support, compared to the use of qualitative cultures.
- Mortality was reduced by the use of prompt appropriate microbial agents from the beginning of the therapy.
- The knowledge of local microorganism patterns is important in reducing morbidity and mortality due to VAP.

The evidence present in the above study suggests that (1) invasive modalities for culture of lower respiratory tract secretion are not clearly superior to noninvasive methods for culture of endotracheal secretions; (2) quantitative cultures have no advantage over qualitative cultures in reducing morbidity and mortality in VAP.

In conclusion, the diagnosis of nosocomial pneumonia should be based on an overall perspective of clinical, radiological and bacteriological findings. There is no diagnostic criterion or procedure that serves as a gold standard for the diagnosis of nosocomial (including VAP) pneumonia. There is no definite scientific evidence, or for that matter, expert consensus, to show that antibiotic treatment based on bacteriological examination and cultures of lower respiratory secretions via invasive (special bronchoscopic or other) procedures is superior to empiric treatment aided by culture sensitivity reports on sputum or on tracheal secretions aspirated through a tracheotomy or endotracheal tube.[17-21] Currently, it also cannot be maintained that use of quantitative cultures of endotracheal secretions helps to improve ultimate outcome when compared to qualitative cultures of endotracheal secretions.

The only concession in favor of bronchoscopic diagnostic procedures is that specificity in diagnosis is improved, and perhaps the unnecessary use of antibiotics is avoided for clinically insignificant organisms or in situations where smears and cultures are negative. However, patient outcome has not been altered for the better by the use of diagnostic invasive bronchoscopic or BAL procedures. *In poor developing countries, where cost is important, expertise limited, and when present, not easily available, it is therefore justifiable to treat nosocomial pneumonia (suspected on clinical and radiological evidence) empirically with a suitable planned antibiotic regime. Culture sensitivity of endotracheal secretions in VAP prior to the use of antibiotics is advised.*

Where expense is not in question and the expertise good and available, bronchoscopic BAL or protected BAL, or protected brush specimens are stained and cultured to guide treatment. This option in our opinion is of use only if performed before starting antibiotics. Its efficacy is reduced, if the patient

has already been receiving antibiotics. In any case, empiric therapy with antibiotics should commence promptly after the bronchoscopic procedure. *Treatment should never await culture reports.* A positive Gram stain could however guide initial treatment. Treatment could be later modified, based on culture sensitivity reports.

In our unit, we use empiric antibiotic therapy for nosocomial pneumonia. Bacteriologic examination of tracheal aspirates by semiquantitative culture is done routinely before starting empiric antibiotic therapy, but it is a moot point as to what extent this helps management and patient outcome. We use PSB sampling to obtain more specific bacteriological evidence if a patient on empiric therapy fails to improve. The PSB sampling is done before changing the antibiotic regime. Again, it is doubtful if this protocol influences patient outcome. *Invasive sampling of lower respiratory secretions in nosocomial pneumonia (including VAP) is advised in immunocompromised patients where infection due to opportunistic organisms is a strong possibility. Opportunistic infection is often missed if non-invasive sampling is performed.*

ANTIBIOTIC THERAPY IN NOSOCOMIAL PNEUMONIAS

Though antibiotic therapy to start with is empiric, the selection of antibiotic therapy for each patient should depend on—

- A knowledge and awareness of the prevalence of core organisms and their sensitivity to various antibiotics in a particular ICU setup.
- Clinical background, in particular, the presence of risk factors for MDR pathogens.
- Time of onset of the VAP.
- Whether the patient had received antibiotics prior to the onset of pneumonia.

Awareness of the Prevalence of Core Organisms in a Particular Unit and Their Sensitivity to Different Antibiotics

Core organisms responsible for nosocomial infection in units all over the world are predominantly Gram-negative bacteria. It is the exact prevalence of different Gram-negative organisms and their varying sensitivity to antibiotics that is important. This prevalence and sensitivity to antibiotics may vary from unit to unit. Also, prevalence and sensitivity patterns may vary in the same unit from time to time. A bacteriologic surveillance in every ICU is therefore of crucial importance, and the awareness of the nature of organisms generally responsible for VAP in a unit is of help in choosing appropriate antibiotic therapy.

It needs to be repeatedly stressed that there is a marked increase in the incidence of extended spectrum beta lactamase (ESBL) Gram-negative organisms in many ICUs all over India, particularly in the large metropolitan cities of the country. This is largely due to a lack of antibiotic policy in most ICUs all over the country.

Box 3: Important risk factors for multiple drug resistance (MDR) pathogens

- Antibiotic therapy within the past 90 days
- Current hospitalization of 5 days or more
- Marked severity of the critical illness
- High frequency of antibiotic resistant organisms
- Immunocompromised patients
- Patients with comorbid states
- Multiple invasive procedures

Box 4: Clinical features of severe nosocomial pneumonia

One or more of the features listed below—

- Respiratory failure
- Rapid radiographic progression
- Severe sepsis with hypotension and/or multiorgan failure
- Acute renal failure requiring dialysis

Clinical Background[5,24]

- The feature which is of utmost importance is to determine the presence or absence of risk factors for MDR pathogens. Important risk factors for MDR pathogens are antibiotic therapy within the past 90 days, current hospitalization of 5 days or more, and a high frequency of antibiotic resistant organisms in a particular ICU or hospital. Other risk factors include immunosuppressed patients, patients with comorbid states, in particular, severe chronic obstructive pulmonary disease (COPD). Risk factors for MDR pathogens are listed in Box 3.
- *The severity of the VAP whether mild to moderate or severe* Severe nosocomial pneumonia is characterized by one or more of the following features—respiratory failure, rapid radiographic progression, severe sepsis with hypotension and/or multiorgan failure, acute renal failure requiring dialysis (Box 4).
- In VAP, the time of onset of nosocomial pneumonia—whether early onset or late onset helps guide the nature of empiric therapy.

Use of Antibiotic Therapy Prior to the Onset of VAP

- This factor if present further guides the nature of empiric therapy.
- Principles in treatment strategy in VAP and factors contributing to treatment strategy are listed in Boxes 5 and 6.

In patients with early onset VAP who have not received antibiotic therapy, the etiological bacteria often found are *Enterobacteriaceae*, *Haemophilus sp*, or *S. pneumonia*. Monotherapy with a third generation cephalosporin with no anti-pseudomonal activity (e.g. cefotaxime or ceftriaxone), or the use of clavulinic acid with amoxicillin is appropriate in these patients for about 7 days (Table 4).

In contrast, VAP occurring in patients after prolonged ventilator support (late onset) and after prolonged use of

Box 5: Principles in treatment strategy in VAP

In a suspected VAP—
- Promptly start empiric antibiotic therapy after—
  - Sending respiratory secretions (collected by whichever method) for culture antibiotic sensitivity and Gram stain (see text)
  - Blood culture
- Avoid repeating the same antibiotic class if patient has received it in the past two weeks
- Subsequent modification of antibiotic regime as per culture sensitivity
- Persevere with the same antibiotic regime if there is a good clinical response even if this is contrary to culture reports
- Avoid prolonged use of antibiotics
- Consider de-escalation of therapy in appropriate cases
- Stop antibiotics if no growth reported—unless the patient has severe sepsis and no other cause for sepsis is evident

Box 6: Factors contributing to treatment strategies

- Prevalent microbes and their sensitivity in a particular ICU
- Presence or absence of risk factors
- Previous antimicrobial therapy
- Clinical severity
- Time of onset after mechanical ventilation
- Results of culture sensitivity of lower respiratory tract secretions or endotracheal aspirates
- Clinical response

Table 4: Initial empiric antibiotic therapy in nosocomial and VAP of early onset with no risk factors for MDR organisms

Probable organisms	*Recommended antibiotic (any one of the following may be used)*
S. pneumoniae *Haemophilus influenzae*	Ceftriaxone or Amoxicillin-clavulanic acid
Enterobacteriaceae	Piperacillin + Tazobactum

Table 5: Initial empiric therapy for nosocomial or ventilator associated pneumonia of late onset or with risk factors for MDR infection and any degree of severity

Probable organisms	*Recommended antibiotic*
Enterobacteriaceae *Ps. aeruginosa* *Acinetobacter baumannii* Other Gram-negative bacilli	Cefepime or Piperacillin-tazobactam or Carbapenem (Imipenem/Meropenem)

1. The choice of the antibiotic among those listed will depend on the prevalence of the organisms and their sensitivity in a particular unit and also the severity of the disease.
2. Empiric therapy in severe nosocomial pneumonia or when MDR organisms are suspected should include two or more antibiotics, not to prevent resistance for which there is also no convincing evidence, but to provide a wide coverage for all likely infecting organisms.
3. For a wide spectrum coverage of Gram-positive and Gram-negative organisms, a combination like Piperacillin-tazobactam + vancomycin/teicoplanin OR a carbapenem + vancomycin/teicoplanin is recommended.
4. In case of MDR pseudomonas or acinetobacter, add colistin to any of the above antibiotics, preferably to a carbapenem for maximum synergistic activity.
5. If MRSA is suspected in the unit, add vancomycin to the above antibiotics.

antibiotics is often caused by multi-resistant pathogens such as *P. aeruginosa*, *Acinetobacter spp.*, Klebsiella or methicillin-resistant *Staphylococcus aureus* (MRSA). The appropriate antibiotic choice should be one which acts against ESBL producing Gram-negative organisms and against Pseudomonas (piperacillin/tazobactum or carbapenems). Vancomycin may be added if a staphylococcal infection is suspected (Table 5).

In patients with early onset VAP who have received antibiotics, Gram-negative organisms (*P. aeruginosa* and/or other Gram-negative core organisms), as also *Streptococci spp.* and *H. influenzae* are often responsible for the infection.

Finally, in late onset pneumonia occurring without antibiotic use during 15 days prior to infection, Enterobactericeae, Pseudomonas or Acinetobacter and MRSA are often causative agents.

In both the above groups, i.e. early onset with previous antibiotic therapy and late onset without antibiotic therapy, an appropriate antibiotic choice would be a combination of an anti-Pseudomonal β-lactam with Vancomycin to cover MRSA. If nosocomial pneumonia is thought to result from aspiration of stomach contents, or if there is any other reason to suspect anaerobic infection, metronidazole or clindamycin should be added to the antibiotic regime.

Information obtained from Gram stain of respiratory secretions can guide empiric antibiotic therapy The presence of chiefly Gram-positive bacteria should direct treatment towards *Staphylococcus*, *Streptococcus*, and *Pneumococcus*. The morphology of stained organisms is also of help in identification. Predominant Gram-negative bacilli direct an appropriate choice of antibiotics. Empiric therapy should start promptly without awaiting culture reports.

Information obtained from culture sensitivity reports Though both sensitivity and specificity in identification of the etiological agent in nosocomial pneumonia leave much to be desired, the culture report may be valuable in patient management, particularly if the empiric therapy decided upon does not prove beneficial.

Table 6: Recommended dosage of antibiotics for initial empiric treatment

Antibiotic	*Dose (IV)*	*Infusion time*
Ceftriaxone	2 gm 12 hourly	½–1 hour
Cefotaxime	2 gm 6 hourly	½–1 hour
Ceftazidime	2 gm 8 hourly or 12 hourly	2–3 hours
Cefepime	1–2 gm 8 hourly	2–3 hours
Imipenem	1 gm 8 hourly	1 hour
Meropenem	1 gm 8 hourly	3 hours
Piperacillin tazobactam	4.5 gm 6–8 hourly	3 hours
Amikacin	750 mg	Over 20 minutes
Vancomycin	1 gm 12 hourly	3 hours
Linezolid	600 mg 12 hourly	1 hour
Ciprofloxacin	400 mg 8 hourly	1 hour

Abbreviation: IV, intravenous.

Follow-up of Nosocomial Pneumonia after Initiating Empiric Therapy

Once culture sensitivity results are obtained, the antibiotic regime should be adjusted as per the microbiological results. If the organism is resistant to one of the two antibiotics in use it should be omitted. In critically ill patients another antibiotic which acts against the organism may be substituted for the one omitted. The recommendation to omit aminoglycosides after the first 4 days depends on the gravity of the clinical condition. Monotherapy may be justified in patients who show well marked improvement within 4 days (Table 6).

Duration of Therapy

A large prospective multicenter trial[25] which compared the efficacy of 8 days to 15 days duration of antibiotic therapy in VAP concluded that an 8-day regimen resulted in reduced antibiotic use, and a decrease in the emergence of multi-resistant bacteria when compared to the 15-day regime, without altering the prognosis. It must be remembered that the above is a study on a large group and is not necessarily applicable to an individual patient. Each patient must be considered in relation to several factors which may be applicable to him or her. It is impossible to stop treatment after 7 days or even 15 days in severe *P. aeruginosa* or *Acinetobacter spp.* infections. It is often necessary to continue treatment for several weeks if there is evidence of breakdown of lung tissue with one or more abscesses or in presence of an empyema or in the presence of persistent intra-abdominal sepsis.

If however a sharp clinical improvement occurs within the first 3–4 days of therapy, if PaO_2 and oxygen requirement improve significantly and inflammatory markers [C-reactive protein (CRP)] sharply decline, antibiotics could be withdrawn safely after 7–10 days.

Lack of Response to Antimicrobial Therapy

There are several reasons for a lack of response to antibiotic therapy. These include a wrong diagnosis of pneumonia, or lack of specific antibiotic coverage against the causative organism. At times though the choice of antibiotic therapy is correct, persistence of the etiological agent leads to a persistent or worsening pneumonia. Persistence of the offending microorganism may be due to several factors; an important cause is inappropriate dosing regime.

Superinfection pneumonia is a serious problem that often causes death. Superinfection follows prolonged broad-spectrum antibiotic therapy. Organisms causing superinfection are generally drug-resistant and therefore lethal. They include resistant strains of Pseudomonas and other Gram-negative bacteria, MRSA, *Enterococci*, fungi and MDR *Enterobacteriaceae*.

Nosocomial pneumonia when severe can lead to multi-organ dysfunction and/or septic shock, situations where the mortality is high in spite of adequate antibiotic therapy.

PROGNOSIS AND MORTALITY[26,27]

Nosocomial pneumonia is the leading cause of death due to hospital-acquired infections. Mortality rate ranges from 20% to 70%. High-risk organisms that lead to increased mortality include *P. aeruginosa*, *Acinetobacter spp.*, *Enterobacter spp.*, other Gram-negative organisms, *S. faecalis, S. aureus, Candida* species, *Aspergillus spp.* and polymicrobial infections. The development of VAP is accompanied by a 1.8–4 fold increase in the risk of death. A French study[26] noted that mortality was inversely related to adequacy of the initial empiric antibiotic therapy. Luna and colleagues[27] found an overall mortality of 52.6% in 76 mechanically ventilated patients with bacteriologically confirmed VAP if the choice of the initial antibiotic therapy was not appropriate and there was a delay in the start of therapy. *Substituting a correct antibiotic cover after culture sensitivity reports are available does not reduce mortality if the initial empiric therapy has been inadequate.*

It must be however remembered that nosocomial pneumonia is more common in patients who are critically ill with multiple problems. To what extent death can be attributable to nosocomial pneumonia per se may be impossible to judge. *It is likely that many critically ill patients die with pneumonia rather than die of pneumonia.*

Death in nosocomial pneumonia can result from any one or more of the following—septic shock, multiple organ dysfunction, ARDS, cardiovascular instability, GI bleed. In VAP, it could also be occasionally related to pneumothorax or other forms of barotrauma.

Ventilator-Associated Tracheobronchitis (VAT)

Not all ventilator associated pulmonary infections constitute pneumonia. They could take the form of a tracheobronchitis characterized by the presence of purulent secretions without any parenchymal involvement. The frequency of VAT is less than VAP, but VAT often progresses to VAP. The microbiology of VAT is the same as VAP and can include MDR organisms. Systemic antimicrobial therapy is indicated in VAT.

Box 7: Prevention of nosocomial pneumonia

- Implementation of educational programs for caregivers and frequent performance feedbacks and compliance assessment
- Strict alcohol-based hand hygiene
- Avoidance of tracheal intubation and use of NIV when indicated
- Daily sedation vacation and implementation of weaning protocols
- No ventilator circuit tube changes unless the circuit is soiled or damaged
- Aspiration of subglottic secretions
- Oral care with chlorhexidine
- Avoid stress ulcer prophylaxis in very low-risk patients for gastrointestinal bleed, and consider use of sucralfate when indicated
- Semi-recumbent patient positioning
- Postpyloric feeding in patients who have impaired gastric emptying

Abbreviation: NIV, noninvasive ventilation.

Aerosolized therapy with antibiotics (notably gentamycin) perhaps prevents the occurrence of VAP.

PREVENTION OF NOSOCOMIAL PNEUMONIA (BOX 7)

Effective measures to prevent nosocomial pneumonia would reduce the incidence of a disease which is associated with a high morbidity and mortality. The Institute for Healthcare has recommended that infection control measures of proven efficacy should be grouped and implemented as a bundle rather than being implemented individually. This policy has led to better outcome; significant reductions in the incidence of VAP have been reported following the implementation of VAP preventive bundles.[28]

General Prophylactic Measures

General prophylactic measures play an important role. These in brief include—

- Educating all ICU personnel including residents on various aspects of VAP and on the preventive strategies that reduce its incidence. It is important to constantly maintain this high level of education and ensure that there is perfect compliance in relation to execution of preventive strategies.
- *Handwashing* The World Health Organization (WHO) considers alcohol-based hand disinfection as the single most important strategy to prevent healthcare associated infection[29] and most studies carried out in ICUs have confirmed the marked reduction of nosocomial infection if alcohol based hand hygiene is religiously implemented.
- *Daily Interruption of Sedation* Daily interruption of sedation avoids constant and continuous impairment of respiratory defense mechanisms. It should be practised as a general rule with very few exceptions. Avoidance or a sparing use of neuroparalytic agents has also been recommended.
- Both tracheal intubation and mechanical ventilator support predispose to VAP and the longer the period these interventions are in place the greater the incidence of VAP. As a corollary the patient should be weaned off support and extubated as soon as it is safe to do so. There are a number of intensivists who opine that protocol-driven weaning procedures help early extubation. Yet there are some intensivists who opine that early extubation compatible with good patient outcome and safety may also be achieved without following rigid protocols.
- Noninvasive ventilation has the advantage of obviating the use of an endotracheal tube. The risk of nosocomial pneumonia is thereby reduced. Noninvasive ventilation is particularly useful in acute exacerbations of COPD causing acute respiratory failure, and in respiratory failure due to pulmonary infection in immunocompromised individuals.
- *Improved Design of Tracheal Tube Cuff* Improved design and special material in tracheal tube cuffs have been put into practice with a view to reduce the likelihood of aspiration of infected secretions across the cuff. The new material used for tracheal cuffs include polyurethane, silicone and latex.
  Before the tracheal tube cuff is deflated, it is important to aspirate secretions in the oropharynx. It is equally important to aspirate tracheal secretions through the tracheostomy tube no sooner than when the cuff is deflated.
  Coating the internal surface of the endotracheal tube with antimicrobial agents such as silver has been proposed to prevent biofilm formation within the tube. This is a theoretically sound innovation but we have no experience of its use.
- *Aspiration of Subglottic Secretions* Subglottic secretions are often colonized and aspiration of colonized secretions through colonized endotracheal tubes reduces hydrostatic pressure above the cuff and prevents leakage of infected supraglottic secretions across the cuff. Aspiration could be through continuous or intermittent suction. Current evidence recommends intermittent suction every 4–6 hours over continuous suction, in order to avoid the potential risk of tracheal injury.
- *Endotracheal Tube versus Tracheostomy* Opinions and practices vary in different ICUs. We have always encountered an increased frequency of complications if an endotracheal tube remains in situ for over 10 days. We replace it with a tracheostomy. In patients with voluminous tracheobronchial secretions effective suction through an endotracheal tube is often not very effective. In these patients a tracheostomy is advised as it allows better suction, less retained secretions and less chances of areas of infected atelectasis.
- *Management of Ventilator Circuits* Ventilator circuit changes should not be made frequently. It is recommended that heated humidifiers be replaced by heat and

moisture exchangers as the former are more likely to be contaminated with microorganisms.

Closed tracheal suction systems have no advantage over open suction. In fact, in patients with excess tracheobronchial secretions, closed system suction is ineffective and is likely to lead to an increased chance of infection.[30]

- ❑ *Use of Propped up or Semi-recumbent Position* The patient is best kept with the head of the bed at an angle of 45°. A randomized trial[31] showed a decrease in the incidence of VAP with patients ventilated in a semi-recumbent position compared to patients ventilated in the supine position. This is a simple but important preventive measure against VAP.

Stress Ulcer Prophylaxis

The general consensus is that prophylaxis of stress ulcers should be provided by the use of sucralfate as this does not raise the pH of gastric contents. H_2 receptor antagonists and proton pump inhibitors raise the pH of gastric contents and thereby promote increased colonization within the stomach. Aspiration of colonized gastric contents into the respiratory tract can lead to nosocomial pneumonia.

Enteral feeding has been considered a risk factor for nosocomial pneumonia because of increased risk of alkalization of gastric contents, and aspiration of gastric contents. Yet it is unquestionably preferred to IV alimentation which poses a greater risk for bloodstream infection.

Many critically ill patients have delayed gastric emptying. Placing the feeding tube beyond the pylorus reduces but does not obviate the risk of aspiration nosocomial pneumonia.

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Care over Orophyngeal Secretions

Oropharyngeal secretions in critically ill patients in the ICU are invariably colonized by pathogenic Gram-negative bacteria which could be aspirated into the lungs. Use of 2% chlorhexidine to clean the oropharynx is a simple but important method to reduce the incidence of aspiration pneumonia. This should be done frequently in all patients and is of particular importance in patients with poor oral and dental hygiene.

Gastric Decontamination

Selective decontamination of the GI tract has been used for many years as a preventive strategy for nosocomial pneumonia. Antibiotics used are non-absorbable—tobramycin, polymyxin, amphotericin B; they are introduced through the nasogastric tube into the stomach in order to prevent gastric colonization with Gram-negative and *Candida spp.*, while preserving the anaerobic flora. Gastric decontamination as a prophylactic measure against nosocomial pneumonia is often used in the ICUs in Europe. The potential risk of breeding antibiotic resistant organisms is genuine and results of randomized trials remain controversial.

General Patient Care

Patients should be turned frequently; physiotherapy to the chest, deep breathing, increased mobility in bed, all help to prevent atelectasis and infection. Meticulous asepsis should be observed during suction of tracheal secretions.

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INTRAVASCULAR CATHETER-ASSOCIATED BLOODSTREAM INFECTIONS

Central venous catheters (CVC), Swan-Ganz catheters and intra-arterial catheters are frequently used in the monitoring and management of patients in the ICU. These catheters provide for the infusion of fluids and electrolytes, for the infusion of antimicrobial agents, for short-term hyperalimentation and for hemodynamic monitoring in critically ill individuals.

Besides the use of CVCs, which provide direct access to the large veins in the chest, teflon or other synthetic short catheters are often inserted into peripheral veins for the infusion of fluids and the intravenous administration of drugs and into an artery for monitoring arterial blood pressure. The intravenous and intra-arterial access provided in ICU patients by catheters for purposes stated above is for a short-term period. They are ordinarily removed as soon as the critical phase of the patient's illness is over.

Central venous catheters used over a long period are of the Hickman type. These are used primarily for the administration of chemotherapy, and for total parenteral nutrition that needs to be continued for weeks or even months. Long-term catheters have a subcutaneous tunnel through which the catheter passes after entering the skin, before entering a large central vein.

Though gaining vascular access is often a necessary and essential feature of critical care, it is associated with a substantial risk of iatrogenic bloodstream infection (BSI) originating from infection of the percutaneous intravascular device (IVD), used for vascular access—IVD related (IVD-R) BSI. This is often referred to as line sepsis.

Intravascular devices are responsible for close to 60% of all bacteremias,[1] and studies performed a decade ago showed that IVD-R BSIs are associated with an increased mortality ranging up to 35%.[2] IVD related BSIs are also responsible for increased length of hospital stay and increased costs.[2,3]

The goal of the intensivist is to promptly diagnose and effectively treat these infections. Equally and perhaps more importantly, it is crucial to prevent them. Based on epidemiological research and on increasing knowledge of the pathogenesis of device-related BSI, guidelines for prevention have been formulated.

A central line associated BSI is defined as an infection related to a central line that has been in situ 48 hours prior to the development of the BSI. It is not considered to be secondary to other sources or sites of infection.

PATHOGENESIS

An intravascular device associated BSI can result from one or more of the three sources listed below—

1. Colonization of the IVD, resulting in a catheter-related infection.
2. Infection of the fluid infused through the IVD, i.e. through the catheter.[4]
3. To produce a catheter-related infection microorganisms must gain access to its extraluminal or intraluminal surface. Three possible mechanisms are involved for this to come about—
   a. Skin organisms gain access to the percutaneous tract, possibly by capillary action and colonize the external surface of the catheter.
   b. Microorganisms contaminate the catheter hub and lumen when the catheter is inserted over a guidewire or is then manipulated. The catheter hub and lumen may also be contaminated by an unsterile infusate.
   c. The catheter tip or body or both may be seeded by microorganisms originating from a distant source (e.g. intra-abdominal sepsis, pneumonia).

This seeding could either be a mere colonization of the catheter tip, or it could be the source of secondary sepsis and septicemia. Hematogenous seeding of the catheter tip is common in patients with severe abdominal sepsis (e.g. septic peritonitis) even in the presence of negative blood cultures. More often than not, this merely represents colonization of the catheter tip rather than a catheter-related sepsis. Seeding of the catheter tip could also occur from organisms which gain entry into the bloodstream through the gastrointestinal tract. This translocation of bacteria from the gut into the bloodstream occurs when there is an overgrowth of pathogenic bacteria in the gut. This is observed in critically ill individuals, particularly in patients whose gastric acidity is sharply reduced by H_2 antagonists and antacids. In many such very ill patients the mucosal barrier of the gut is devitalized or has small breaks which allow the overgrowing bacterial flora to enter the blood stream.

Once the catheter is contaminated and colonized either extraluminally or intraluminally, the microorganism becomes incorporated into a biofilm that leads to persistent infection and hematogenous dissemination.[5] A biofilm is a complex matrix consisting of polysaccharides, proteins and nucleic acid which are derived from both the host and microorganisms. The microorganisms are encased in this biofilm and are therefore less susceptible to antimicrobials and host immune responses.[6,7]

Peripheral IV catheters, arterial catheters, non-tunneled central line catheters are IVDs generally used for a short period of time—less than 10 days. Bloodstream infections related to these are usually due to microorganisms gaining access to the extraluminal surface of the catheter through the skin site of insertion. Occasionally, they may gain access intraluminally following insertion with the guidewire.[8,9]

Table 7: Important risk factors for intravascular device related bloodstream infections

Underlying disease	*Catheter-related factor*
Severe illness with high APACHE score	Clumsy or difficult insertion
Neutropenia	Insertion into the femoral vein or artery
Immunocompromised patient	Poor catheter care
Transplant patient	Occlusive dressing
Prolonged ICU stay	Duration of catheter >7 days
Source of sepsis, e.g. Intra-abdominal suppuration	Parenteral nutrition
Massive surgery	
Mechanical ventilation	
Prolonged use of systemic antibiotics	

Abbreviations: APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit.

In contrast, BSIs caused by long-term (>10 days) IVDs such as cuffed Hickman and Broviac-type catheters, hemodialysis catheters, subcutaneous central venous ports are most often due to contamination of the catheter hub and luminal fluid.[10]

It is important to remember that contamination of parenteral fluids, blood products, IV medications can also cause BSIs particularly with arterial catheters used for long-term hemodynamic monitoring, as also with Hickman catheters, central venous hemodialysis catheters and subcutaneous central venous ports.[11,12]

Most nosocomial epidemics of infusion-related BSI are due to contamination of infusate by Gram-negative organisms introduced during manufacture or during its preparation and administration.

RISK FACTORS (TABLE 7)

A number of risk factors can be identified. The severity of the illness influences the risk, patients who are severely ill with high Acute Physiology and Chronic Health Evaluation (APACHE) scores carrying a significantly greater risk for BSIs. Neutropenia, immunocompromised patients, human immunodeficiency virus (HIV) patients, transplant patients all carry a greater risk of IVD-R BSIs. The longer the stay in the ICU, the greater the risk for all nosocomial infections.

A multilumen catheter offers more portals for entry of infection than a single lumen catheter. Also multilumen catheters are generally inserted in more severely ill patients who are subjected to more interventions leading to an enhanced risk of infection.

Catheters introduced into the jugular vein are more frequently associated with infection compared to subclavian vein catheters. This could be related to increased motion at the jugular vein site and the difficulty in keeping this site clean due to soiling with oropharyngeal secretions.

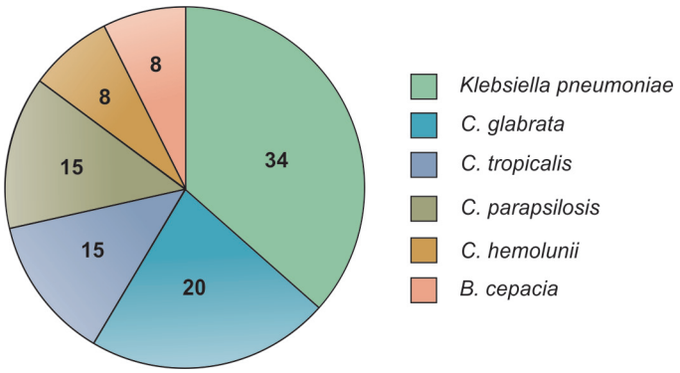

Fig. 6: Percentage (%) distribution of central line-associated bloodstream infection (CLABSI) pathogens in 2012 at the Breach Candy Hospital

The longer a catheter remains within a vein, the greater the risk. Repeated catheterization also increases the risk. It is unwise to change a central line catheter every few days; yet it is equally unwise to keep the catheter in for weeks with intent to change it only when infection occurs. Each ICU may frame its own rules; we prefer to change the central line every 8–10 days.

It has been shown that the features of the IVD, its insertion and maintenance significantly influence the risk of infection. Merrer and colleagues[13] showed that insertion of an IVD in the femoral vein versus the subclavian vein was associated with a far greater risk of infection (20 vs 3.7 BSIs per 1,000 IV device days), and far more thrombotic complications (21.5 vs 1.9%).[13] Risk of catheter-related BSI increases in the presence of a suppurative focus in the body, as it exposes the catheter to bacteremia. Occlusive dressing over the site of puncture for CVC or any IVD can lead to a growth of microorganisms and predispose to infection at the site of entry.

Training, efficiency and care shown by the medical and nursing staff as also the nurse to patient ratio in the ICU (ideally 1:1) and the cleanliness of the environment (so important to consider in developing countries) all play a role in the incidence of blood stream device-related infection in an ICU. Important risk factors for IVD-R BSI are tabled in Table 8.

MICROBIOLOGY

The microbiology of IVD-R BSI varies from one geographic area to another and for that matter in different ICUs in the same city.

The microbial profile of IVD-R BSI based on an analysis of 159 published prospective studies in America[14] showed that the commonest microorganism causing BSI was the coagulase negative *Staphylococcus spp.* (31%) followed by *S. aureus* (18%), enteric Gram-negative bacteria (14%), *Pseudomonas aeruginosa* (8%), *Candida species* (6%), Corynebacterium species (5%), *Enterococcus species* (4%), miscellaneous (4%).

The microbial profile at the Breach Candy Hospital for central line associated bloodstream infection (CLABSI) in the year 2012 is illustrated in Figure 6.

DIAGNOSIS

Before attributing fever or features of sepsis to an IVD-R bloodstream infection, it is important to thoroughly examine the patient and assess the possibility of all other likely sources of infection commonly observed in critically ill patients in the ICU. These include urinary tract infection, nosocomial pneumonia in particularly a ventilator-associated pneumonia (VAP), surgical site infection, colitis caused by *C. difficile,* sinusitis related to a nasotracheal intubation, infected bed sores. Recent evidence-based guidelines provide current information on the evaluation of a patient in the ICU who presents with pyrexia or other signs of sepsis.[15]

If after a thorough clinical examination and relevant tests the cause of pyrexia is not evident, or there are features of sepsis without any identifiable cause, the likelihood of an IVD-R bloodstream infection is strong. In the presence of inflammation at the catheter site insertion, (particularly if there is purulence), together with fever and features of sepsis, an IVD-R bloodstream infection is extremely likely and the intravascular device should be promptly removed.

Another indication of an IVD-R bloodstream infection is blood cultures repeatedly positive for organisms such as *Staphylococci spp., Corynebacterium spp.,* or bacillus species or *Candida spp.,* or *Malassezia spp.*

Blood Cultures

Blood cultures are basic investigations in the diagnosis of IVD-R bloodstream infections. There are several features which need to be stressed in relation to this crucial investigation—

- Empiric antibiotic treatment for a presumed BSI in a critically ill patient should never be started without obtaining prior blood cultures. The blood culture should always be taken from two separate sites, at least one of which is drawn from a peripheral vein by percutaneous venipuncture.
- The sensitivity of blood cultures, which means the greater yield of positive blood culture, is enhanced significantly if a larger volume of blood is drawn for each culture. In adults, 30 mL of blood should be drawn for each blood culture—15 mL being inoculated into aerobic and 15 mL into anaerobic medium.
- Blood cultures drawn through CVCs offer good sensitivity for BSI but are less specific compared to cultures obtained from peripheral veins.[16,17]
- A thorough cleansing of the skin before drawing blood for culture from a peripheral vein is vital, so as to avoid contamination and misleading results. The antiseptic solution recommended is chlorhexidine, tincture of iodine, isoprophyl alcohol, and povidone iodine combined with alcohol rather than povidone iodine alone.
- Up to 30% of blood cultures positive for *S. epidermidis* (an organism commonly present on the skin) represent true infection. However, a single positive culture invariably is due to contamination. This again illustrates the importance of collecting blood cultures (using adequate quantity of blood) from two separate sites whenever BSI is suspected.
- If blood cultures from the IVD (e.g. a central line catheter) and a peripheral vein are positive, the IVD should be removed.
- If either one or the other is positive and no other source of infection is evident, it is again best to remove the IVD.
- In a critically ill individual running undiagnosed fever or having features of sepsis the IVD is best removed, if there is clearly no other source to explain the above findings even if blood cultures from both sites are negative. Abolition of the unexplained fever and regression of sepsis after removal of an IVD such as a CVC may be the only proof of IVD-R bloodstream infection.

Cultures of the Removed Intravascular Device

Culturing the removed intravascular device is the gold standard for IVD-R bloodstream infection, particularly for a short-term (<10 days) IVD. Catheter segments can be cultured semiquantitatively on solid media or quantitatively in liquid media (removing the adherent organisms by sonication).[18,19] The higher the colony count the greater the probability of line sepsis. A growth equal to or greater than 15 colony-forming units (CFU) from a 5-cm catheter segment cultured by semi quantitative method, or growth equal to or greater than 10^2 CFU from a catheter segment cultured by the quantitative method denotes catheter-related infection if the patient had local signs of inflammation or signs of sepsis. If there is significant growth in the absence of local inflammation or sepsis, it denotes colonization of the IVD. If it is necessary to insert a new device it is best to insert it at a new site, rather than inserting one in the same location over a guidewire.

Quantitative or semiquantitative culture methods are generally preferable for detecting infection in IVD that are in place greater than 10 days. This is because the route of infection in long-term devices is generally hub contamination with intraluminal colonization and infection. The quantitative method removes organisms (through sonication) from both external and internal surfaces of the catheter.

The semiquantitative method is often preferred for short-term (<10 days) intravascular devices as the route of infection is generally an ascending infection from the site of skin puncture ultimately colonizing the external surface of the catheter. The semiquantitative method is cheap, less expensive and gives a quicker result.

Gram stain of intravascular catheter segments of removed catheters shows an excellent correlation with results obtained from quantitative methods and allows a quick diagnosis of catheter infection.

Diagnosis of an IVD-R Bloodstream Infection When the IVD Is in Place Longer Than 10 Days

An IVD in place longer than 10 days includes CVC, Hickman and Broviac catheters, hemodialysis catheters and central venous ports. Persistent fever or features of sepsis without any other cause has prompted removal of these devices.

Only 15–45% of these devices removed for suspected infection are found to be colonized or infected at the time of removal. Removal of a Hickman catheter or hemodialysis catheter when they are not infected raises unnecessary difficulties. Quantitative or semiquantitative blood cultures drawn from the IVD (e.g. a central line catheter in place >10 days or a Hickman catheter >10 days) and concomitantly drawn cultures from a peripheral vein allow a diagnosis IVD-R blood stream sepsis—bacteremia or fungal, with a sensitivity and specificity of 80–95%[20] without removal of the catheter, provided empiric antibiotics have not been started.

- If both IVD drawn blood culture and peripheral vein drawn blood culture are positive for the same microorganism and if the growth in blood drawn from the IVD shows at least threefold higher concentration of microorganism per mililiter compared to that grown from the venipuncture an intravascular device-related bloodstream infection is confirmed.
- The other criteria used for diagnosing IVD-R bloodstream infection is the differential time to positivity (DTP) of paired blood cultures—one drawn from the IVD and the other concomitantly from the peripheral vein. If the blood drawn from the IVD comes positive 2 or more hours before that drawn from the peripheral vein a BSI can be confidently diagnosed. The sensitivity and specificity of this test ranges from 82% to 94%.[20]

The differential time positivity test has been tried out in patients with short-term IVDs with disappointing results. This is as expected, since the route of infection in a short-term IVD is extraluminal.

Detection of Contaminated Infusion

If the infusion is suspected to be contaminated the proof lies in demonstrating a growth of the same organism from the infusate and from culture of the peripheral blood.

COMPLICATIONS OF CATHETER-RELATED SEPSIS

Other than varying grades of bacterial sepsis, the two major complications are (1) a septic thrombophlebitis and (2) disseminated fungal infection.

Septic peripheral thrombophlebitis is obvious by the signs of inflammation and thrombosis of peripheral veins. Thrombophlebitis in central veins is often difficult to diagnose. Edema proximal to the phlebitis is common and should promptly arouse suspicion. Localized pain, warmth and tenderness are the important features, particularly when the internal jugular vein is involved. Blood cultures continue to be positive, and features of sepsis persist after removal of the catheter. Venography of a central vein may confirm the diagnosis. Small pulmonary emboli may complicate the picture, and in one of our patients, sudden death occurred from pulmonary embolism, the source of embolism being an infected clot in the subclavian vein.

Disseminated fungal infection is often missed. It should always be suspected when fever and other features of sepsis continue in spite of removal of the catheter and the use of appropriate antibiotics. This is of particular importance in neutropenic or immunocompromised patients. Fever persisting for more than 3 days in spite of the administration of broad-spectrum antibiotics and catheter removal in a critically ill neutropenic patient should prompt a trial with amphotericin B.

TREATMENT

Entry Site Infections

Short-term catheters suspected to be infected should be removed, but it would be unwise to remove a long-term Hickman's catheter as this catheter is often used as a lifeline for chemotherapeutic drugs and/or for hyperalimentation in very sick individuals. Entry site infection of long-term catheters should be treated with local bactericidal ointments and antibiotics given orally or intravenously. The choice of antibiotics depends on the organisms grown, aided by antibiotic sensitivity results.

Tunnel Infection

Patients with tunnel infection (e.g. with Hickman's catheter) require removal of the catheter. The tunnel needs to be surgically opened and the infection drained. One should not wait for culture reports before starting antibiotics. The antibiotic regime should preferably include vancomycin for a possible staphylococcal infection, and a third generation cephalosporin active against *P. aeruginosa* and other Gram-negative infections, or an aminoglycoside.

Catheter-Related Sepsis

Short-term catheters are promptly removed and antibiotics given. We prefer to give antibiotics for a period of 5–10 days depending on the clinical response. Empiric therapy generally includes a third generation cephalosporin (ceftazidime or cefoperazone) with an aminoglycoside. If features of sepsis persist, methicillin or vancomycin is added. The frequency of infection due to methicillin-resistant *Staphylococci* is still low in our unit. In other units, particularly in oncology units, the incidence is high, necessitating the empiric use of vancomycin till blood and catheter tip culture sensitivity reports are available. If catheter sepsis is proven on culture reports, or is strongly suspected, and if the patient worsens in spite of using a broad-spectrum antibiotic cover, a decision to start amphotericin B should be taken.

Septic thrombophlebitis, particularly of central veins, requires the use of IV heparin in addition to an appropriate combination of antibiotics as stated above.

PREVENTION

The Healthcare Infection Control Practices Advisory Committee has recently released guidelines for the prevention

Table 8: Summary of recommendations from guidelines for prevention of intravascular catheter-related infection (2011)

Subject	*Recommendation*
Placement of central venous catheter	Use ultrasound guidance to place central venous catheters to reduce the number of cannulation attempts and mechanical complications (category IB)
Skin preparation	Use 0.5% chlorhexidine for skin preparation and dressing changes. If there is contraindication for chlorhexidine, use tincture of iodine or 70% alcohol (category IA)
Catheter site dressing regimens	Use a chlorhexidine impregnated sponge dressing for temporary short-term catheters in patients older than 2 months of age if CLABSI is not decreasing despite adherence to basic prevention measures (category IB)
Patient cleaning	Use 2% chlorhexidine wash for daily skin cleaning (category II)
Catheter securement device	Use sutureless securement device to reduce the risk of infection for intravascular catheters (Category II)
Antimicrobial lock solutions	Use prophylactic antimicrobial lock solution in patients with long-term catheters who have a history of multiple CRBSI despite optimal maximal adherence to aseptic technique (category II)
Antimicbrobial impregnated central venous catheters	The use of a chlorhexidine or silver sulfadiazine impregnated or minicycline or rifampicin impregnated catheter is recommended in patients whose catheter is expected to remain >5 days, again if the optimal recommended measures have not produced a fall in BSI rates
Needleless intravascular catheter systems	Use a needleless system to access IV tubing (category IC). When a needleless system is used, a split septum valve may be preferred over mechanical valves, due to increased risk of infection with the mechanical valves (category II)
Performance improvement	Use hospital specific or collaborative based performance improvement initiatives in which multifaceted strategies are bundled together to improve compliance with evidence-based practices (category IB)

Abbreviations: CLABSI, catheter line-associated bloodstream infection; CRBSI, catheter-related bloodstream infection.
Source: O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52(9):e162-93.

of intravascular catheter-related infections. They stress that the program to prevent catheter line associated bloodstream infection (CLABSI) be a multidisciplinary approach.[21] The new guidelines recommend using performance improvement initiatives to decrease CLABSI rates and increase compliance with evidence based practices. Similar to the published guidelines in 2002 the new recommendations emphasize the education of healthcare workers and the assessment of knowledge and adherence to guidelines for those involved in the insertion and maintenance of CVCs. The new guidelines also discuss the use of new technologies to further reduce CLABSI. A statement is also included regarding the importance of ensuring trained, competent and appropriate nursing staff levels, as elevated patients to nurse ratio is associated with an increase in the rate of CLABSI.

Alterations in clinical practice and education interventions have clearly made a very favorable impact on the incidence of hospital acquired infection over the last decade in the West. The Pittsburg Regional Healthcare initiative introduced multiple control interventions to reduce the rate of CLABSI starting from 2001. From 2001–2005, the pooled rate of CLABSI in the participating ICUs reduced by 68%.[22]

The Michigan Health and Hospital Association Keystone ICU project is another large scale quality improvement initiative to reduce hospital acquired infection. During the initial study period starting from 2004 and extending one and a half years the CLABSI rates decreased by 66%. These results were sustained for a further 18 months after completion of the study.[23]

The interventions in both these studies focused on hand hygiene, the use of chlorhexidine for skin preparation, the use of full barrier precautions during insertion, the use of the subclavian vein as the preferred insertion site and the removal of unnecessary CVCs.

There is also an encouraging study carried out by the International Nosocomial Infection Control Consortium (INICC). They studied the effects of the implantation of a comprehensive strategy on CLABSI rates in the intensive care units of twelve developing countries. With an emphasis on education, feedback of outcome, surveillance (infection rate) and process surveillance (adherence to infection control measures) the CLABSI was significantly reduced. It dropped over a period of 24 months from 16.4–7.4 CLABSI per central line days. The number of deaths due to CLABSIs was reduced by 58%. These results are indeed encouraging. With a little more effort, results will hopefully yet improve.[24]

The updated recommendations of the new guidelines are set out in Table 8.

Technology Innovations in the Prevention of CLABSI

New technological innovations have come to the forefront to help further reduce CLABSI. These include—

- Use of real time ultrasound guidance to help insert the central line. Ultrasound guidance reduces the number of cannulating attempts, thereby reducing the risk of mechanical complications, when compared to insertion of central lines using the help of anatomical landmarks.
- Use of antimicrobial and antiseptic impregnated catheters. The lumen of the CVC is filled with an antimicrobial

solution which is allowed to remain when the catheter is not in use. These catheters are expensive and perhaps should be restricted to patients who have long-term CVC in place, and who have repeated BSIs in spite of optimal standard care. The use of a chlorhexidine or silver sulphadiazine impregnated or minicycline or rifampicin impregnated catheter is recommended in patients whose catheter is expected to remain greater than 5 days, again if the optimal recommended measures have not produced a fall in BSI rates.

- The new Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines recommend the use of chlorhexidine impregnated sponge dressing in patients older than 2 months if in spite of optimal efforts the rate of BSI does not decrease.
- A chlorhexidine (≥2%) daily skin wash instead of a soap and water skin wash is a simple strategy that has led to reduced BSI rates in the ICUs.
- The use of sutureless securement devices for intravascular catheters is now recommended as a category II recommendation. Use of these devices may reduce catheter colonization by maintaining the integrity of the surrounding tissues.

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URINARY CATHETER-ASSOCIATED INFECTIONS

Till recently, UTIs headed our list of nosocomial infections as in most ICUs all over the world. However, in the last three years, there has been a dramatic fall in UTIs due to the active surveillance measures taken by the hospital staff. The most important predisposing factor for such infections is the presence of an indwelling urinary catheter.[1] Urinary infection is catheter-acquired if it develops while a urinary catheter is in situ or within 72 hours of its removal.[2] The longer a catheter remains in the bladder, the greater the risk of urinary infection. Unfortunately, the use of urinary catheters for long periods of time in very ill individuals is often necessary. The incidence of bacteriuria from urinary catheters varies from 5% to 10% per day.[1] In our experience, a growth of organisms in urine is present in almost every patient who has an indwelling catheter for more than 8 days. Many of these are asymptomatic, but a fair number are symptomatic. As with all nosocomial infections, it is difficult to distinguish between colonization by bacteria and actual infection. The Infectious Disease Society of America[2] has laid down guidelines to distinguish catheter-related asymptomatic bacteriuria from catheter-related urinary tract infections. Urinary infection may take the form of a cystitis or urethritis or may involve the upper urinary tract and produce pyelonephritis.

PATHOGENESIS[2,3]

Bacteriuria

A urinary catheter aids entry of microorganisms into the bladder through several mechanisms. The most common mechanism is the ascension of a biofilm (containing microorganisms) along the catheter which when it reaches the bladder results in a bacteriuria. The bacteriuria is well correlated with the duration of catheterization.[4] Bacterial presence in the periurethral area could allow these microorganisms to be pushed into the bladder during catheter insertion. If these microorganisms persist bacteriuria results. When the catheter is not managed properly, or when contaminated urine in the bag refluxes into the bladder, organisms can again reach the bladder. Organisms may also be introduced when there is a break in the tubing system. Finally, the bulb of the indwelling catheter does not allow a complete drainage of the urine. A small pool of urine remains; once organisms reach this retained pool of urine, or the biofilm on the catheter or bladder wall they persist and multiply.

A biofilm is an inevitable sequel of an indwelling catheter. Host proteins adhere to the surface of the catheter wall forming a conditioning layer. This layer facilitates adherence of microorganisms which generate a polysaccharide coating under which the bacteria grow. They are now less vulnerable both to antibiotics or the host immune response. This biofilm extends both in the inside and outside of the catheter wall and also along the bladder wall. Hydrolysis of urea in the urine by urease producing bacteria such as *P. mirabilis* leads to an alkaline environment with precipitation of calcium and magnesium, so as to result in a crystalline biofilm.[5] This material is similar to urinary bladder and renal stones; it can cause encrustation and block the catheter.

Symptomatic Infection

Factors determining symptomatic catheter-related urinary infection are not clearly understood. Mucosal trauma during catheterization or mucosal bleeding are known to precede fever and bacteremia from a urinary source but symptomatic episodes related to the above are comparatively small in number. Urinary obstruction due to a completely or partially blocked catheter is one other factor leading to symptomatic infection. Nicolle[3] believes that though the virulence of organisms in the bladder, which has an indwelling catheter cannot be disregarded, this does not play a pivotal role. She noted that *E. coli* grown from bacteriuria resulting from a catheter-related bacterial infection as also that grown from the blood in patients with asymptomatic bacteriuria show an attenuation of virulence properties.

MICROBIOLOGY[2,3]

An analysis of urine cultures in individuals with catheters in our ICU showed that the commonest organism grown was *E. coli* followed by *Enterococci spp.*, *Klebsiella spp.*, *P. mirabilis*, *P. aeruginosa* and Enterobacteriaceae. A growth of *Candida spp.* is not at all uncommon in very ill patients with indwelling catheters who have been deluged with powerful broad-spectrum antibiotics.

Gram-positive organisms, such as coagulase negative *Staphylococci* and *Entercoccus* species are isolated frequently but are not usually associated with symptomatic infection. Bacterial isolates from critically ill patients are generally characterized by increased bacterial resistance. Extended β-lactamase producing Gram-negative bacteria are commonly found.

Polymicrobial infections are also fairly frequent in catheterized patients. The presence of polymicrobial infections in the urine in non-catheterized patients, or in those who have not had any instrumentation done on their urinary tract, is likely to be due to contamination.

The microbial profile at the Breach Candy Hospital for urinary tract infection (UTI) in year 2012 is illustrated in Figure 7.

RISK FACTORS

Risk factors for catheter-induced bacteriuria (often accompanied or followed by infection) are prolonged duration of catheterization, a break in the closed system drainage with colonization of the urinary bag, poor catheter care, urethral trauma, a raised serum creatinine, diabetes, preuretheal

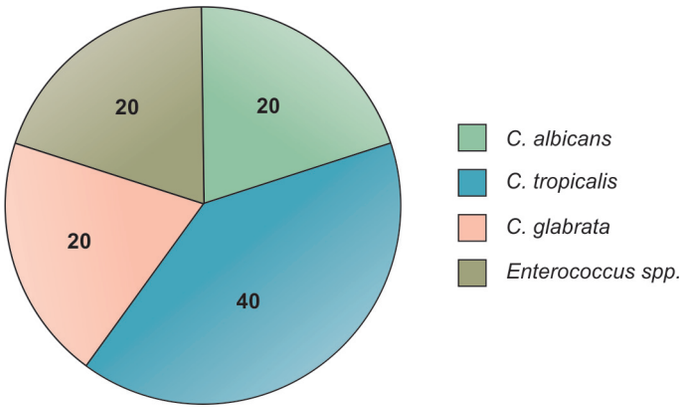

Fig. 7: Percentage (%) distribution of catheter-associated urinary tract infection (CAUTI) in 2012 at the Breach Candy Hospital

colonization with potential pathogenic bacteria and immunocompromised states.

CLINICAL FEATURES[2,6]

Signs and symptoms of catheter-associated urinary infection include new onset or worsening of fever, rigors, delirium, lethargy, suprapubic pain or discomfort. Hematuria, pain and/or tenderness over the costovertebral angle may also be observed.

In patients in whom the catheter has been removed, dysuria or urgency and frequency of urine or suprapubic pain denote a catheter-associated urinary infection.

A search for a possible urinary tract infection is mandatory in a patient with clinical features of sepsis, or in one who has pyrexia for which there is no other apparent cause.

Infection may be mild, moderate or fulminant in nature. Fulminant Gram-negative infections produced by catheter-related *P. aeruginosa* or *Klebsiella spp.*, or any other Gram-negative infections may take the form of high fever with severe rigors, and may quickly progress to a state of mental obtundation, hypotension, septic shock and renal failure. A rapidly progressive renal insufficiency may be the sole clinical manifestation of a severe catheter-related urinary tract infection, both in very critically ill patients and in immunocompromised states.

COMPLICATIONS

These include pyelonephritis, emphysematous pyelonephritis, renal abscess, perinephric abscess, Gram-negative bacteremia with septic shock. Progressive renal failure may complicate urinary tract infections, and this is often compounded by the use of nephrotoxic drugs (e.g. aminoglycosides) used to treat such infections.

DIAGNOSIS[2,3]

Catheter-associated urinary tract infection (CA-UTI) must be distinguished from catheter-associated asymptomatic bacteriuria. The International Clinical Practice Guidelines from the Infectious Disease Society of America give the following definitions for catheter associated urinary infection and catheter associated asymptomatic bacteriuria (CA-ASB).

CA-UTI in patients with an indwelling urethral catheter is defined by the presence of symptoms or signs compatible with UTI with no other identified source of infection, along with more than or equal to 10^3 CFU/mL of more than or equal to 1 bacterial species in a single catheter urine specimen, or in a midstream voided urine specimen from a patient whose urethral or condom catheter has been removed within the previous 48 hours.

CA-ASB in patients with an indwelling urethral catheter is defined by the presence of more than or equal to 10^5 CFU/mL of more than or equal to one bacterial species in a single catheter urine specimen in a patient without symptoms compatible with UTI.

Criteria for symptomatic catheter-related urinary tract infection have also been laid down by the National Healthcare Safety Network (NHSN).[6]

NHSN Criteria for Catheter-Related Urinary Infection

At least one of the following signs or symptoms with no other recognized cause—

Fever >38°C, suprapubic tenderness, costovertebral angle pain or tenderness,

OR

For patients <1 year of age, one spike of fever (>38°C core), hypothermia (<36°C core), apnea, bradycardia, dysuria, lethargy or vomiting,

AND

Urine culture with ≥10^5 CFU/mL with no more than two species of organisms,

OR

Urine culture with ≥10^3 CFU/mL with no more than two species and a positive urine analysis [positive dipstick for leukocyte esterase or nitrite, pyuria (≥10 WBC/mm^3 or ≥3 white blood cells/HPF unspun urine)], microorganisms in Gram stain of unspun urine.[6]

Guidelines from the Infectious Society of America and from NHSN are not exactly similar. This is perhaps an illustration of trying to gather, equate and practice all clinical medicine solely from the available evidence.

What Should the Practicing Intensivist or Physician Do?

I would consider that in the presence of clinical features of urinary tract infection, the presence of a urine culture showing a 10^5 CFU/mL could indicate a catheter-related UTI. There is an important proviso to the above statement. In critically ill patients with fever, patients with ongoing or increasing sepsis where no other cause is evident, the presence of pus cells in urine and a urine culture with greater than 10^5 CFU/mL warrant treatment. It is perfectly possible for a urinary infection in the above circumstances to be the cause of sepsis and we have witnessed this in critically ill patients with the above-mentioned features.

Urine Examination[2,3]

Pyuria[2]

A patient with a catheter-associated UTI must have pyuria. The absence of pus cells in a symptomatic patient should suggest a diagnosis other than a UTI. The presence, absence or degree of pyuria by itself should not be used to distinguish CA-ASB from CA-UTI.

In CA-UTI the urine should show greater than or equal to 3 WBC/HPF in unspun urine. Pus cells can be quantified by using a hemocytometer. Pus cells greater than or equal to 10 WBC/mm^3 are significant. The NHSN criteria suggest that a positive dipstick for leukocyte esterase or nitrite is also significant as is the presence of microorganisms in a Gram stain of unspun urine.

Culture[2,3]

Empiric antibiotic therapy should never be given before sending for a urine culture. One however must not await culture reports in critically ill patients to start treatment.

If a short-term indwelling catheter is in place the urine for culture should be collected through puncture of the sampling port. Urine collected through the catheter will show a higher colony count if the catheter is lined by a biofilm. For the same reason if the urinary catheter has been in place for a long time, greater than 2–3 weeks, the catheter should be replaced by a new catheter and urine specimen for culture should be sent from the newly inserted catheter.[7]

Patients with a short-term indwelling catheter who have symptoms of urinary infection have quantitative counts greater than or equal to 10^5 CFU/mL.[8] Lower quantitative counts may be observed when patients are having diuresis or receiving antimicrobial therapy. Lower counts may occasionally represent early biofilm contamination of the catheter.

For patients with a long standing indwelling catheter who have symptoms of urinary infection, a quantitative count of greater than 10^5 CFU/mL of one or more organism is also appropriate for a diagnosis of culture-associated infection.

When urine culture shows a colony count of less than 10^5 CFU/mL in a patient with an indwelling chronic catheter attribution of fever to a UTI is in doubt and the diagnosis should be critically reassessed.

Urine cultures for bacteria or fungi submitted to the microbiology laboratory should be processed promptly. Alternatively, the specimens should be stored at 4°C; at this temperature the organisms remain viable for about 24 hours. If urine sent to the laboratory is kept standing for over 2 hours before being cultured, the urinary bacterial count increases significantly, thus making the diagnosis of urinary infections increasingly difficult. Sensitivity tests to antibiotics are routinely performed whenever the colony count is greater than 100,000 CFU/mL. When a polymicrobial flora is grown, sensitivity tests for different organisms may need to be performed separately.

Other Laboratory Investigations

A blood count may show leukocytosis and blood cultures may detect bacteremia, the source being an infected urinary tract.

Imaging Studies

Patients in the ICU with urosepsis, whether catheter-related or not, often require evaluation for upper urinary tract disease. Ultrasonography (USG) is useful to establish the anatomy of the kidneys, and to exclude an obstructed ureter. Occasionally, an IV or retrograde pyelography may be necessary. A computed tomography (CT) scan may establish the diagnosis of a suspected renal or perinephric abscess and may yield further evidence of any ureteric obstruction.

Differential Diagnosis

It is important as stated earlier to distinguish urinary tract colonization manifested by asymptomatic bacteriuria from a true UTI. Prostatitis, pelvic inflammatory disease and diverticulitis may mimic a catheter-related urinary tract infection in a very ill individual. Not uncommonly, a septic state in a moribund patient in the ICU is mistakenly attributed to the presence of a comparatively mild to moderate urinary infection, whereas the actual cause is more sinister, e.g. an intra-abdominal abscess or a peritonitis resulting from a bowel perforation or infarction.

TREATMENT

Bacteriuria in Asymptomatic Patients[9]

Antibiotic therapy should not be used as bacteriuria will often recur after antibiotics are stopped, or superinfection with more virulent organisms may occur. There is also the fear and concern of selection of antibiotic resistance.[9]

Prophylactic use of antibiotics in patients having an indwelling urethral catheter is not recommended in the guidelines but is often used in many ICUs in the hope of preventing UTI.

Bacteriuria in Symptomatic Patients[2,3]

In symptomatic patients, the catheter is removed and suitable antibiotics commenced. If the patient needs an indwelling urinary catheter, a new one is inserted. In serious UTIs, it is important to commence therapy promptly after sending urine cultures in patients who appear very ill, without waiting for the culture reports. Empiric therapy for urinary infection should also be given in those patients who are hemodynamically unstable, in the immunocompromised and neutropenics, in poorly controlled diabetics, in patients with damaged or prosthetic valves (for fear of complicating bacterial endocarditis), and in patients with deteriorating renal function. The optimal duration of antimicrobial therapy is debatable. If the catheter remains in situ, a 7-day course is recommended to avoid the emergence of resistant organisms.

Selection of Antibiotics

A Gram stain of the urine may help decide the nature of the infection (whether Gram-negative as is common, or Gram-positive in occasional cases), well before culture reports are available.

The choice of antibiotics for Gram-negative infections in most units is usually amoxicillin-clavulanic acid or ceftazidime or cefoperazone, combined with an aminoglycoside. It is best to avoid the latter if renal function is impaired, more so as facilities for determining aminoglycoside levels are not available in all medical centers in the country. Ciprofloxacin is added to ceftazidime or cefoperazone in severe UTIs with renal insufficiency if sensitivity reports support its use. An alternative regime for severe Pseudomonas or other Gram-negative infection is the use of piperacillin-tazobactam combination or of merepenem.

Currently, there has been a great increase in ESBL producing organisms resistant to penicillins and third generation cephalosporins, so that in many patients one has to resort to the use of carbapenems, or even colistin if cultures show the presence of carbapenem-resistant organisms.

In Gram-positive infections, amoxicillin-clavulanic acid is generally used till such time as a culture report is available. Resistant staphylococcal infections are not common in our unit. If however infection with resistant *Staphylococci* is suspected, the drug of choice is vancomycin, which covers both resistant *Staphylococci* as well as *Enterococci*. Gentamicin may be added for mixed staphylococcal and Gram-negative infections.

Candiduria[10]

The presence of candida in the urine requires careful interpretation.

Asymptomatic candiduria in an immunocompetent patient generally indicates mere colonization without infection. It clears when the catheter is removed and particularly when the antibiotics are stopped.

Symptomatic candiduria in immunocompetent patients or severe candiduria, even though asymptomatic in immunocompromised individuals, often spells danger. It could signify fungal infection of the bladder, an ascending fungal pyelonephritis, or disseminated candidiasis. The presence of disseminated candidiasis is difficult to diagnose as blood cultures are not necessarily positive. Fluffy white retinal exudates protruding from the retinal surface into the vitreous, and an endophthalmitis have been reported in 40–50% of patients with disseminated candidiasis, but we have never had the opportunity of observing these lesions. Clinical features that should make one suspect disseminated candidiasis are—

- A deterioration in the general condition with worsening renal function in a patient with persistent and profuse candida in the urine.
- Growth of *Candida spp.* from two other sites (e.g. sputum, vascular catheter), besides the urine. In neutropenic patients who are septic, growth of *Candida* from just two sites is sufficient evidence to start systemic antifungal therapy.
- Profuse growth of *Candida* in the urine in a patient who has no indwelling catheter or pus cells in the urine of a patient who is deteriorating clinically at a very rapid rate.

Treatment

Suspected Candida infection of the upper urinary tract or suspected disseminated candidiasis requires the use of IV fluconazole or IV amphotericin B (see Chapter Invasive Fungal Infections in the ICU). The indwelling catheter should be removed and a new one inserted, if a catheter is vital for patient management.

Candidiasis confined to the bladder should be treated with oral fluconazole and/or irrigation of the bladder with amphotericin B. Sobel[10] describes the following method for irrigation of the bladder with amphotericin B solution. 50 mg amphotericin B is mixed with 1 L of sterile water and infused at a rate of 40 mL/hour, using a three-way bladder catheter. The response is generally good and the irrigation can be stopped after 3–4 days. Systemic candidiasis or fungal involvement of the kidneys or the perinephric space requires the prompt use of amphotericin B.

PREVENTION OF URINARY CATHETER-RELATED INFECTIONS[2,6,11,12]

Measures to prevent catheter-related infection, if assiduously practiced, can sharply reduce the incidence of these infections. This reduction can also happen in poor developing countries of the world as is shown by a study of catheter associated urinary tract infection rates in adult intensive care units of 15 developing countries.[13] A multidimension infection control strategy consisted of a "practice bundle" with details on education and training on the insertion, care and maintenance of the urinary catheter, outcome surveillance, process surveillance, hand hygiene compliance, urinary catheter care monitoring and performance feedback. In phase I of this study (before intervention) the CA-UTI rate was 7.86 per 1,000 urinary catheter days. In phase II after intervention the CA-UTI decreased to 4.95 per 1,000 catheter days—a significant 17% reduction.[13]

The reader is referred to the 2009 International Practice Guidelines for the details on the prevention of catheter-associated urinary tract infection (Boxes 8 and 9). A few important and relevant aspects are given below—

- Insert an indwelling catheter only if absolutely necessary. If condom drainage of the urine is satisfactory, and there is no urinary retention, it is wiser not to insert the catheter. The catheter should be removed as soon as it is not needed.[2]

  About 20–50% of indwelling catheters in patients in ICU do not meet the appropriate indications for catheter insertion, and 30–50% of catheter days are reported to be unjustified because the catheter remains in situ beyond which is necessary.[12]

  Strategies to reduce the use of catheterization have been shown to be effective and have a greater impact on reducing nosocomial UTI than any other strategy advised in the guidelines.
- A urinary catheter must be inserted under complete aseptic conditions, and should be meticulously cared for once inserted.

Box 8: Indications for indwelling catheter (Healthcare Infection Control Practices Advisory Committee)

- Acute urinary retention or bladder outlet obstruction
- Accurate measurement of urine output in critically ill patients
- Selected perioperative use—
  - Urologic or genitourinary surgery
  - Prolonged duration of surgery
  - Large volume infusions or diuretics during surgery
  - Intraoperative monitoring of urine output
- Assist in healing open sacral or perineal wounds in incontinent patients
- Prolonged immobilization for spine or pelvic fractures
- Comfort for end-of-life care

Source: Gould CV, Umscheid CA, Agarwal RK, et al. Guideline for prevention of catheter-associated infections. [online] CDC website. Available from http://www.cdc.gov/hicpac/ [Accessed September 2013].

A closed catheter drainage system with ports in the distal catheter for needle aspiration of urine should be used to reduce CA bacteriuria and CA-UTI in patients with an indwelling urethral or suprapubic catheter. Disconnection of the catheter junction should be minimized and the drainage bag and connecting tube should always be kept below the level of the bladder.

The catheter should not be pulled upon during nursing, and the sterile system should not be broken by obtaining samples of urine for examination from the urine collection bag. Urine samples should always be obtained from the proximal portion of the catheter or through the sample port of the catheter system. The urethral meatus should be coated with a bactericidal ointment—neosporin, soframycin or bacitracin. Care should be taken that the catheter is not contaminated by fecal matter or secretions on bedsheets or bedclothes.

- Antibiotic coated catheters were proposed to reduce the incidence of CA-UTI. Current studies show that the use of antibiotic coated or silver oxide coated catheter do not reduce the incidence of UTI.[14]
- Complex catheter systems continue to be devised. They have yet to prove their use and the expense plus close attention and supervision necessary, render their use impractical in developing countries.

Box 9: Recommended practices for indwelling catheter insertion and maintenance

- Catheter insertion—
  - Properly trained personnel
  - Hand hygiene
  - Smallest-bore catheter
  - Aseptic technique and sterile equipment
- Catheter maintenance—
  - Sterile, continuously closed drainage system
  - If breaks, replace catheter, collecting system, and connection
  - Consider using preconnected, sealed catheter-tubing junction
- Maintain unobstructed urine flow from bladder to drainage bag—
  - Avoid tube kinking
  - Keep bag below bladder
  - Empty bag regularly
  - Separate collecting containers from each patient
- Standard precautions for catheter and collecting system manipulation

Source: References 2, 6 and 11.

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ANTIBIOTIC-ASSOCIATED COLITIS

GENERAL CONSIDERATIONS

Diarrhea in a patient under critical care is most often due to antibiotics, to overzealous enteral feeding, or following chemotherapy for malignancy or myeloproliferative diseases. In hospitals and ICUs in poor countries, where kitchen hygiene leaves a lot to be desired, outbreaks or isolated instances of intestinal infection due to *E. coli, Shigella spp.*, *Salmonella spp.*, or trophozoites of *E. histolytica* may also be occasionally observed.

Antibiotic-associated diarrhea is due to an overgrowth of various organisms in the gut. An overgrowth of *C. difficile* in the colon can lead to a potentially serious form of diarrhea due to a *C. difficile* infection causing a colitis.[1,2]

C. difficile is a spore bearing anaerobic bacillus that produces Toxin A and Toxin B. A few strains produce only Toxin B. All strains including those only producing Toxin B can cause the same spectrum of illness characterized by an intestinal pathology. Nosocomial hospital outbreaks due to *C. difficile* are assuming increasing importance in hospitals in the West. In our part of the world *C. difficile* infection is fairly frequent but outbreaks of nosocomial infection are uncommon. The increasing incidence of *C. difficile* infection in ICUs in the East is largely due to increasing awareness of the infection.

Non-toxigenic strains of *C. difficile* also exist—they do not produce disease. The difference in the ability to produce toxin is important as some diagnostic tests detect *C. difficile* whether it produces toxin or not, and others test only for Toxin A. The sharp increase of *C. difficile* infection in the West over the last 10 years is due to the emergence of a new strain of *C. difficile,* the BI/NAPI/027 strain. This strain produces more toxins A and B than the usual strain. It also produces a third toxin, a binary toxin which is highly resistant to fluroquinolones.

Exposure to antibiotics is the most common cause of *C. difficile* infection. This is particularly prevalent in ICUs where patients often receive multiple classes of antibiotics. The most common antibiotic associated with *C. difficile* infection is clindamycin, but all broad spectrum antibiotics—ampicillin, augmentin, third generation cephalosporins, and almost all other antibiotics can trigger it. In the West, fluoroquinolones are increasingly associated with it due to the emerging strain BI/NAPI/027 which is highly resistant to this drug. Other risk factors include increasing age, severity of a critical illness and suppression of gastric acid by H_2 antagonists and by proton pump inhibitors. Patients in the same ward, unit or ICU as those suffering from *C. difficile* infection are at greater risk for also acquiring the infection. *C. difficile* infection can thus spread from patient to patient and this fact is crucial in relation to preventive measures to curb spread of the disease.

CLINICAL FEATURES[3]

A low-grade fever and watery diarrhea of varying severity are observed. This may occur during antibiotic therapy, or may occur some weeks after antibiotics have been stopped. The diarrhea may be mild or profuse causing both hypovolemia, and fluid and electrolyte disturbances. Mucus, blood and shreds of colonic mucosa that have sloughed off from the colon, may be present in the stools. The clinical features may be indistinguishable from acute dysentery. Pseudomembranous colitis occurs only in 50% of cases. In severe pseudomembranous colitis, all the features of a toxic megacolon may occur, culminating in perforation of the large bowel. This is more likely if the association of the above clinical features with the antibiotic used is not realized, and the drug is not immediately withdrawn.

DIAGNOSIS[2-5]

The diagnosis is made by detection of *C. difficile* or its toxin in patients with diarrhea. The presence of pseudomembranous colitis is confirmatory for *C. difficile* infection but as mentioned earlier this entity occurs only in 50% of cases. The most commonly used test is a toxin A or B enzyme immunoassay (EIA). Unfortunately this test has variable sensitivity and specificity. Also the Eliza test only detects toxin A and will therefore miss strains that produce toxin B. An EIA test has been advocated in the West for *C. difficile* glutamate dehydrogenase. To the best of my knowledge it is not performed in India except perhaps in special labs. Other lab tests for confirmation are polymerase chain reaction (PCR), or toxigenic culture.

Differential diagnosis includes infective diarrhea or dysentery due to various organisms—*E. coli*, *Shigella*, *Campylobacter jejuni*, *Salmonella* and *E. histolytica*. These nosocomial infections of the gut may be rare in Western countries, but are not so uncommon in our part of the world. In the elderly, a differential diagnosis of ischemic colitis must also be considered. Cytomegalovirus infections in immunocompromised patients may present with diarrhea or with a hemorrhagic colitis. Noninfectious causes of nosocomial diarrhea include enteral feeding, drugs increasing intestinal motility and alteration of the normal bowel flora following antibiotic use.

MANAGEMENT[5,6]

Most patients improve quickly after withdrawing the antibiotic responsible for the diarrhea. Specific therapy must be used in patients with severe diarrhea, or in those whose diarrhea continues after stopping the antibiotic. Drugs useful in

pseudomembranous colitis are metronidazole[5] 400 mg thrice daily for 14 days, or vancomycin 250 mg thrice a day orally for 14 days. Excellent results are generally obtained with metronidazole.

In severe infections associated with hemodynamic instability vancomycin 500 mg qds is given through a nasogastric tube and metronidazole is administered intravenously in a dose of 500 mg 8 hourly. Vancomycin retention enemas 250 mg in 250 mL normal saline four times a day are advised if the patient has an ileus. Intravenous immunoglobulin in a dose of 500 mg/kg for 1–3 doses has also been recommended for fulminant colitis. A surgical consultation should always be sought as some fulminant cases may need a subtotal colectomy.

In patients who have recurrent *C. difficile* infection, the initial oral dose of vancomycin 125 mg 6 hourly should be tapered very slowly over a period of 6 weeks.

C. difficile, at least in Western countries, has been known to survive for prolonged periods on a variety of surfaces—walls, carpets, beds, etc. It is also easily transmitted to patients through the hands of doctors, nurses and other paramedical personnel working in the ICU. Hospital outbreaks can spread from one infected patient to the other in an ICU.[6] Meticulous care—handwashing in particular as also other preventive measures including the implementation of isolation procedures are necessary to prevent this spread.

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PREVENTION AND CONTROL OF NOSOCOMIAL INFECTIONS

(Also see Prevention of Nosocomial Pneumonia, Device related Bloodstream Infections and Urinary catheter–associated Infections)

INFECTION CONTROL AND PREVENTION PROGRAMS[1]

Ideally every hospital should have an Infection Control and Prevention Committee consisting of heads of major clinical services, pathologists, microbiologists, hospital matron, senior sisters of the ICU, registrars and physiotherapists. The basic function of such a committee is outlined in Box 10 and comprises of maintenance of surveillance of nosocomial infections, with special reference to the ICU, and formulation of policies and procedures for prevention and control of such infections. It is imperative to lay down a standard policy for sterilization of instruments and other invasive gadgetry used in the ICU. Frequent checks should be carried out to ensure that strict standards once formulated are meticulously followed.

Frequent educational updates for nurses and house doctors on the correct use and management of invasive devices, or of other devices responsible for nosocomial infection, are of great help. These devices include urinary catheters, all varieties of intravascular catheters, equipment for hemodynamic monitoring and for hemofiltration, tracheostomy and endotracheal tubes, mechanical ventilators, nebulizers and other gadgets used for respiratory therapy.

Box 10: The role of a nosocomial infection control committee

- Surveillance of nosocomial infection, particularly in the ICU
- Formulation of policies and procedures for prevention and control of such infections
- Laying down of a standard, strictly followed policy for the effective sterilization of instruments and other gadgetry used in the ICU
- Holding educational updates for nurses and house doctors on the correct use and management of invasive devices, or of other gadgetry contributing to nosocomial infection (see Text)
- Formulation of a broad policy on the use of antibiotics in the ICU
- Investigation of a nosocomial outbreak
- Implementation of immunization programs (particularly against Hepatitis B virus), and protection against infection (all fulminant infections and HIV infection) of medical, nursing, paramedical and other hospital staff. Special emphasis should be laid on protection of those working in the ICU and other high-risk areas within the hospital

Abbreviations: ICU, intensive care unit; HIV, human immunodeficiency virus.

Instructions on the correct use and handling of gadgetry should be extended to the operating theater staff, with special reference to the cardiopulmonary bypass machine, and the use of the intra-aortic balloon pump.

A policy should be formulated on the use of antibiotics in the ICU, though sufficient latitude needs to be given to the treating consultant within the framework of such a policy.

The Infection Control Committee should shoulder the responsibility of promptly investigating a nosocomial outbreak. Finally, it should supervise and implement immunization programs and protective measures against infection, for the medical, paramedical, nursing and other personnel working in the ICU and other high-risk areas of the hospital.

It is beyond the scope of this chapter to cover and discuss at length the various factors contributing to nosocomial infections in the ICU. Nevertheless, some basic practical points need to be emphasized (Box 5).

Hand Hygiene[2]

Hand hygiene is perhaps the most important measure for preventing nosocomial infection and includes the use of alcohol rubs as well as soap-based agents for handwashing. Hands should be thoroughly washed with soap and water, followed by a hand rub with an alcohol-based agent with or without chlorhexidine before touching or handling a patient in the ICU. Bar soaps easily get contaminated with microorganisms and hence their use must be discouraged. Liquid soap containing dispensers are preferred in the ICU. Washing hands is also imperative before examining or dressing a wound, performing an invasive procedure, or touching invasive devices used in patient care. Hand hygiene should always be performed with an alcohol-based antiseptic when one has finished with the patient, as contamination of the hands with pathogenic organisms will almost certainly have occurred. ICU personnel, in our experience, frequently carry Gram-negative bacilli and *Staphylococci* either on the skin, or nares or within the throat. Yet the habit of handwashing seems extremely difficult to inculcate in all workers (including doctors) in the ICU. Alcohol rubs are advantageous in that they are fast acting (15–20 sec) and have the widest spectrum of activity against various microorganisms. Alcohol rubs are the best in settings where the quality of water cannot be relied upon. When using an alcohol rub, one needs to ensure that the hands are rubbed dry for the rub to be effective in killing the microorganism. As per the WHO recommendations, it is mandatory to wash hands with soap and water when the hands are visibly soiled with organic matter like blood or body

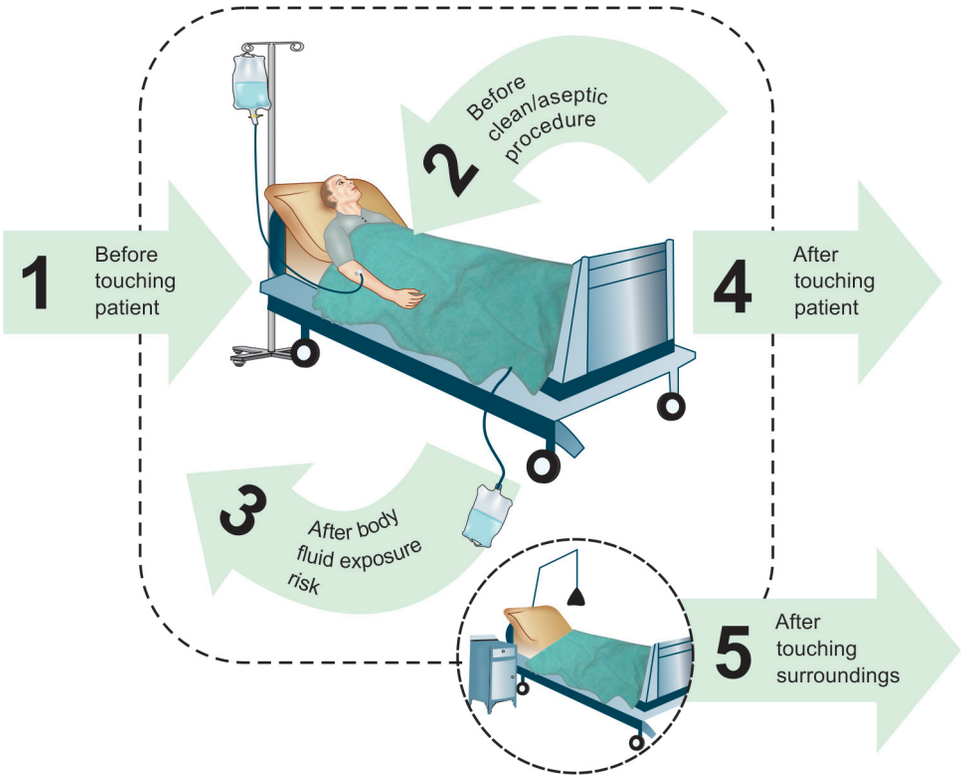

Fig. 8: Five moments of hand hygiene
Source: World Health Organization.

fluids and when caring for patients who are carrying spore bearing organisms like *C. difficile, C. tetani* and others.

The World Health Organization (WHO) recommends the "five moments of hand hygiene" at all times of patient care (Fig. 8).

Use of Reliable Chemical Disinfectants and Antiseptics

Perfect sterilization and disinfection encompass almost all measures aimed at preventing nosocomial infections. The failure of a disinfectant to disinfect reusable respiratory apparatus, ventilator tubings, or a patient's skin prior to an invasive procedure can be responsible for serious outbreaks of nosocomial infection. Contamination of disinfectants and antiseptics leading to nosocomial outbreaks is a well-known phenomenon all over the world.[3] Povidone iodine, a common antiseptic agent used in the ICU has been responsible for four nosocomial outbreaks due to *P. aeruginosa* in the USA.[4] Hence, when suspecting a common source outbreak in the ICU, sampling disinfectants and antiseptics is very important.

Careful Use of Invasive Devices and Other Gadgetry Known to Cause Nosocomial Infections

A few points need to be emphasized—

- It is tempting to use invasive gadgetry just because it is waiting to be used! Developing countries are fortunate in a way because not all ICUs are very well-equipped and invasive monitoring equipment like Swan-Ganz catheters are expensive. With greater experience, invasive monitoring is done only in selected problem patients, in whom diagnostic assessment is difficult, and whose management is therefore uncertain.
- Ventilator tubings should not be changed frequently as was thought earlier. Bacterial filters in ventilators should be changed every 48–72 hours. Every precaution should be taken to prevent nosocomial infections through nebulizers. Nebulizing solutions may sometimes be contaminated and cause nosocomial pneumonia. It is wrong to use nebulizers unless they are of clear benefit to the patient; routine use of nebulizers should be strongly discouraged.
- Central venous lines are removed as quickly as possible. It is best to remove a catheter in the radial artery (used for monitoring blood pressure) by the 5th day. When central lines are suspected to cause nosocomial infection, catheter tips should be cultured in a correct manner (see subsection on Catheter-Related Infections). Blood cultures through a CVC and simultaneously through a peripheral vein help in the diagnosis of device-related blood stream infections.
- Urinary catheters are the commonest cause of nosocomial infections. They should be meticulously cared for.
- Tracheostomy tubes should be changed every 7 days. The no-touch technique for tracheal aspiration through

a tracheostomy tube or through an endotracheal tube is vital. Every single suction should be carried out like a surgical procedure. It is not necessary to wear gloves for suction, but the hands should be thoroughly scrubbed. Sterile gloves however should be worn for changing a tracheostomy tube or for dressing a tracheostomy wound.

Carefully Planned Use of Antibiotics (Also See Use of Antibiotics in the ICU)

An indiscriminate use of antibiotics can cause an ecological disaster, characterized by the multiplication of resistant bacteria in the ICU. This has been observed all over the world. Resistant organisms include methicillin-resistant Staphylococci, Gram-negative bacilli including Proteus, *Klebsiella spp.*, *Enterococci* and *P. aeruginosa* resistant to third generation cephalosporins and aminoglycosides, and fungi, in particular, *Candida*. These resistant organisms cause great problems in management, and are the source of serious nosocomial infections that can wreak havoc in an ICU setting.

Circumspection and Care in Use of Antacids and H_2 Antagonists for Upper GI Bleeding

Since increasing the pH of gastric acid contents by antacids and H_2 antagonists promotes colonization of the stomach, it is wise not to use H_2 antagonists routinely in all critically ill patients as prophylaxis for GI bleeding. Severe GI bleeding due to acute or chronic gastric or duodenal ulcers can however pose a serious hazard to life, and H_2 antagonists with sucralfate are indicated. Some ICUs prefer to use sucralfate alone, as it prevents a significant change in the pH of gastric contents.[5,6]

Good Nutritional Support

This is vital if nosocomial infections are to be successfully treated. In our country, and in all other developing countries, critical illnesses manifest against a background of poor nutrition. Survival for example in severe tetanus or in nosocomial infections complicating severe tetanus, is absolutely impossible without adequate nutritional support.

Isolation of Patients with Fulminant Infections and of Patients Infected by Resistant Bacteria

Barrier nursing and contact isolation are vital features to combat outbreaks of infection.

Cleanliness of ICU Environment

It is vital to keep the ICU environment as physically clean as possible. The practice of changing shoes and wearing special slippers before entering the ICU is an eyewash, and perhaps contributes to additional nosocomial infections. It is more important to have the floor swabbed with a disinfectant every 3–4 hours through the day and night, to keep bedside tables clean and uncluttered, to keep ceilings, walls and curtains meticulously clean, and to have as little equipment as possible cluttering the unit.

Box 11: Prevention of nosocomial infections

- Thorough hand washing
- Use of reliable chemical disinfectants and antiseptics
- Care over central lines or urinary catheters (care bundle strategy) and other invasive devices
- Tracheostomy care and care of ventilator tubings, nebulizers, and all other respiratory equipment
- Judicious use of antibiotics
- Careful use of antacids and H_2-antagonists
- Isolation of patients with resistant bacteria or fulminant contagious infections
- Keep ICU environment as clean as possible
- Good nutritional support

Abbreviation: ICU, intensive care unit.

The incidence of nosocomial infections in an intensive care unit is also dependent on trained nursing staff and the nurse-patient ratio which ideally should be 1:1. The comparatively low incidence of nosocomial infection in our ICU could partly be due to the fact that in our unit, patient care in relation to washing and cleaning is entrusted only to the nurses, who have been indoctrinated and trained to wash hands promptly after touching a patient. IV lines or other invasive and noninvasive gadgets used for patient care are never touched without first scrubbing the hands. Bedpans and urinals are also solely handled by the nursing staff. In contrast, in all or almost all other units urinals and bedpans are handled by a special group of untrained men and women whose standards of hygiene, to say the least, are deplorable.

Selective Decontamination of the GI Tract

(See Prevention of Nosocomial Pneumonia) (Box 11).

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CHAPTER 45

Community-Acquired Fulminant Infections Requiring Critical Care

INTRODUCTION

Important community-acquired fulminant infections requiring critical care in poor developing countries include diseases peculiar to these countries as also diseases which are common to both to the East and West. Important examples of the latter group of diseases are fulminant pneumonia, bacterial sepsis and infections of the neuraxis, all of which have been dealt with in other sections of this book. This section deals with fulminant tropical infections; of these *Pasmodium falciparum* infection leads the list. Other fulminant infections that have been dealt with in this section are tetanus, disseminated hematogenous tuberculosis, complications of severe typhoid fever, fulminant amebic infections, dengue hemorrhagic fever, severe leptospirosis, severe scrub typhus and melioidosis. Each one of these infections presenting in a severe form has a high morbidity and a significant mortality. Prompt diagnosis, early treatment (which to start with is often empiric) and good critical care are crucial for survival.

Fulminant Plasmodium Falciparum Infection—Cerebral Malaria[1]

GENERAL CONSIDERATIONS

Plasmodium falciparum malaria is now unfortunately endemic in many parts of India. It has even become endemic in the city of Bombay (now Mumbai) and its suburbs, and in other major cities of Maharashtra and Gujarat. What is worse; strains resistant to chloroquine are frequently encountered. In certain cities of Gujarat, like Navsari, Surat and Ahmedabad, *P. falciparum* is more often than not resistant to chloroquine.

The global case fatality rate of falciparum infections is around 1% or 2 million deaths per year.[1] *P. falciparum* is the predominant malarial infection in highly endemic areas of Africa,[2,3] and has a high prevalence in South America and Southeast Asia, including India and Thailand.[1-3] Cerebral malaria is the most severe manifestation of *P. falciparum* infection, and is responsible for 80% of 2 million global deaths. If unrecognized and not correctly treated, cerebral malaria is almost certainly fatal. It must however be realized that severe *P. falciparum* infection can also cause death through a fatal involvement of other organ systems, without necessarily producing a significant involvement of the central nervous system.

PATHOPHYSIOLOGY[1,4]

The pathological and clinical manifestations of severe *P. falciparum* infection are caused exclusively by the intraerythrocytic asexual form of the parasite. The parasite exerts a twofold action—

- It induces the formation of protein-rich knobs on parasitized red blood cell (RBC) surface membrane, causing these cells to adhere to the endothelial lining of the microvasculature, through proteins such as thrombospondin, intercellular adhesion molecules and CD36. This cytoadherence leads to a sequestration of the parasitized RBCs in the capillaries and postcapillary venules in the brain and other organs of the body. Obstruction to microcirculation in the brain and other organ systems leads to tissue hypoxia and lactic acid acidosis.
- The interaction between the parasite and the host RBCs is believed to result in the liberation of tumor necrosis factor α, interleukins and other potentially toxic or pharmacologically active compounds such as reactive oxygen species and nitric oxide. These have deleterious local-cum-systemic effects.

It is a combination of the above two factors which is responsible for severe multiple organ dysfunction observed in fulminant falciparum infections. This obstruction to the microcirculation within the brain produces cerebral hypoxia and features of cerebral malaria. Cerebral edema develops in some patients as a terminal event, and is not the chief cause of coma. Global cerebral blood flow is reduced in cerebral malaria, and there is increased cerebral anaerobic glycolysis with an increase in the cerebrospinal fluid lactate concentration.

Widespread damage to endothelial cells can perhaps trigger disseminated intravascular coagulopathy. Decreased antithrombin levels are noted in severe cases, and generally signify a poor prognosis.

Massive intravascular hemolysis with hemoglobinuria is due to heavy parasitemia; hemolysis also occurs in patients with G6PD deficiency, particularly after the use of quinine.

Damage to the alveolar-capillary membrane due to parasitized RBCs obstructing pulmonary capillaries and due to release of cytokines leads to acute lung injury and noncardiogenic pulmonary edema.

Renal failure is an important feature of fulminant infection. Factors producing renal failure include sluggish circulation due to parasitized erythrocytes, renal vasoconstriction, hemoglobinuria and acute glomerulonephritis.

Hypoglycemia is due to parasitemia as also to quinine therapy. Children and pregnant women are particularly susceptible to hypoglycemia which is often asymptomatic. The increased susceptibility in pregnancy is because of pancreatic islet cell hyperplasia, and other metabolic changes associated with the pregnant state.

Translocation of bacterial flora from the gut may be related to mesenteric ischemia produced by parasitized erythrocytes. Gram-negative bacteremia with secondary sepsis may occur. This is especially observed in the "algid" form of *P. falciparum* malaria.

Box 1: Features of severe falciparum infection [World Health Organization (WHO)]

Clinical features—
- Prostration
- Impaired consciousness
- Respiratory distress (acidotic breathing)
- Multiple seizures
- Circulatory collapse
- Pulmonary edema (radiological)
- Abnormal bleeding
- Jaundice
- Hemoglobinuria

Laboratory features—
- Severe anemia (Hb <5 g/dL) or hematocrit less than 15%
- Hypoglycemia (blood glucose <40 mg/dL)
- Acidosis (plasma bicarbonate <15 mmoL/L) or arterial pH less than 7.25
- Renal impairment (urine output <12 mL/kg/hour) or serum creatinine above age-related normal range; persisting after rehydration
- Hyperlactemia [plasma lactate (>5 mmoL/L)]

CLINICAL FEATURES AND COMPLICATIONS[1,5,6]

Severe falciparum infection is characterized by any one or more of the following features—
- A parasite count greater than 15%.
- Cerebral malaria.
- Hematocrit less than 20%.
- Total serum bilirubin greater than 5 mg per cent.
- Gross fluid and electrolyte abnormalities.
- Evidence of multiple organ dysfunction syndrome.
- Temperature greater than 39°C.
- Complicating infection.

The World Health Organization (WHO)[5] has defined severe disease by the clinical and laboratory features shown in Box 1.

CEREBRAL MALARIA

Cerebral malaria can strike with dramatic suddenness, or may be preceded by unremittent fever accompanied by chills or rigors. Usually 10 days after the fever, the patient has a generalized seizure followed by progressive coma. High fever alone can cause delerium and mental obtundation. The term cerebral malaria should be reserved for an encephalopathy due to *P. falciparum* infection, which leads to mental obtundation, often progressing to coma. *P. falciparum* infection can also induce coma which is post-ictal or is due to severe hypoglycemia.

Hyperpyrexia, frequent or rarely continuous seizures, and increasing coma form a triad of symptoms observed in this dreadful disease. Mild neck stiffness is present at times,

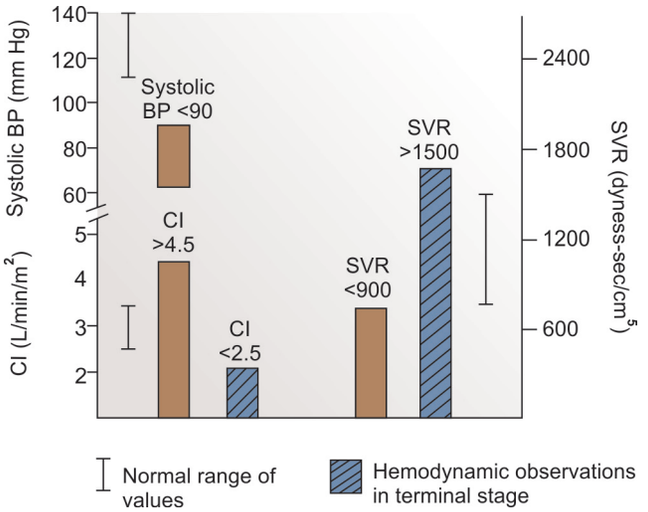

Fig. 1: Hemodynamic observations in fulminant falciparum infections
Abbreviations: CI, cardiac index; SVR, systemic vascular resistance.

Box 2: Pulmonary complications of fulminant falciparum infection

- A fall in PaO_2—inappropriate to the X-ray changes observed
- Acute lung injury of varying severity—
  - Chiefly a V/Q abnormality
  - A marked right to left shunt
- Aspiration pneumonia
- Fulminant pulmonary edema due to hyperpyrexia
- Pulmonary edema due to fluid overload
- Tachypnea with respiratory muscle fatigue
- Nosocomial pneumonia
- Pulmonary embolism

and Kernig's sign may be positive. There is generally no focal neurological deficit. Papilledema is generally absent, but retinal hemorrhages may be seen. Dysconjugate gaze disturbances and in particular skew deviation of the eyes are common, but except in terminal cases the pupillary and corneal reflexes are preserved. Doll's eye movements and oculovestibular reflexes are also generally preserved. Muscle tone is increased, deep jerks are exaggerated, abdominal reflexes are absent, and the plantars are often bilaterally extensor. Extensor thrusts resembling decerebrate rigidity, associated oculogyric crisis, and stertorous breathing may occur in patients who are severely hypoglycemic.

A rare presentation of falciparum malaria is cerebellar ataxia, without disturbance in consciousness. Similar cerebellar signs may be observed in patients recovering from cerebral malaria.

Malarial psychosis is on rare occasions a presenting feature of the disease, though more often than not psychosis follows upon the use of mefloquine or chloroquine.

Fundus examination in adults with cerebral malaria may show retinal hemorrhage, exudates and papilledema. In African children with cerebral malaria retinal changes include macular and retinal peripheral whitening, vessel changes (orange vessels and capillaries whitening) collectively termed malarial retinopathy.[7] We have never observed these changes described in African children in our part of the world.

Fulminant *P. falciparum* infection often produces multiple organ dysfunction, and in our experience 80% of patients with cerebral malaria have complications pointing to other organ system involvement. As has already been pointed out, some patients have severe multiple organ dysfunction without significant cerebral encephalopathy.

Hypoglycemia is very frequent and can occur spontaneously in severe infections with heavy parasitemia, or can occur within a few hours to a few days of starting quinine. Pregnant women and children, as mentioned earlier, are very prone to this complication. Complicating bacteremia also contributes to and worsens the condition.

Patients admitted to ICUs following *P. falciparum* infection occasionally present with hypotension and shock (algid malaria). Diarrhea and severe gastrointestinal (GI) bleeds are often associated features. This state is believed to be due to Gram-negative endotoxemia, probably due to translocation of bacteria from the gut.

The cardiovascular manifestations[8] are often similar to those observed in endotoxin shock, and are typically characterized by hypotension, a lowered systemic vascular resistance (SVR) and an increased cardiac index (CI). A low CI with an increased SVR may be observed in terminally ill or in fulminant cases and is of ominous significance (Fig. 1).

The pulmonary manifestations[8,9] of the fulminant form of the disease are characterized by the evolution of acute lung injury which may be mild, moderate or severe in intensity. The severe form of the disease is associated with a large right to left shunt in the lungs and is generally fatal. Acute pulmonary edema sometimes occurs suddenly and is observed with hyperpyrexia greater than 107°F; this is generally fatal within a few hours. Pulmonary edema also occurs terminally in a number of patients dying of falciparum infection.

Aspiration pneumonia is frequently seen in fulminant infections; nosocomial pneumonia may also occur particularly in patients on ventilator support. Other pulmonary complications include pulmonary edema due to fluid overload and the occurrence of marked tachypnea even in the absence of acute lung injury or acute respiratory distress syndrome (ARDS). Tachypnea in old, feeble and malnourished patients with hyperpyrexia invariably leads to respiratory muscle fatigue and respiratory arrest. Elective intubation and respiratory support is life-saving in these patients. Rarely death may occur from pulmonary embolism. The pulmonary complications of fulminant falciparum infection are listed in Box 2.

The renal manifestations include oliguria, a rise in serum creatinine, and a mild-to-moderate renal insufficiency. Acute tubular necrosis with renal shutdown is occasionally observed, particularly in the presence of hemolysis.

Acute hemolysis can also occur in patients who do not have a G6PD deficiency, and who have not received quinine. It is probably due to heavy parasitemia. Classical blackwater fever is the association of hemoglobinuria with severe manifestations of *P. falciparum* infection in a non-immune patient, who is not G6PD deficient.

Spontaneous bleeding from gums and the GI tract may be encountered. Fulminant malaria can also produce generalized bleeding due to a disseminated intravascular coagulopathy.

Jaundice is frequently present with the serum bilirubin being generally elevated to about 5 mg/dL, and this is accompanied by a modest rise in the serum transaminases. Deepening jaundice (serum bilirubin >15 mg/dL), with a disseminated intravascular coagulopathy initially mistaken as viral hepatitis or obstructive jaundice, is an occasional presentation.

Splenic rupture is an uncommon complication; it can occur even after minor trauma, and is rarely spontaneous, perhaps due to sudden acute splenic enlargement.

Hyponatremia [due to inappropriate antidiuretic hormone hypersecretion (SIADH)], and a lactic acid acidosis are seen quite frequently in severe infections.

Multiple organ systems are often involved with increasing dysfunction, failure and ultimate death. In hyperfulminant cases, death may ensue within 24 hours.

Diagnosis[1,10]

The clinical picture of an encephalopathy or of an encephalopathy with multiple organ dysfunction, should point to cerebral malaria particularly in an area endemic for *P. falciparum* infection. The spleen may or may not be palpable. In fulminant cases, there is probably no time for the spleen to enlarge. A palpable liver and spleen in the presence of the clinical features described above are useful pointers to the correct diagnosis. Repeated blood smears for malarial parasites should be done, and when a clinical diagnosis is highly suspect, specific treatment for falciparum infection should be promptly started. Diagnostic tests to confirm or establish any other diagnosis producing a similar clinical picture must be persisted with. It must be remembered that at times (on rare occasions), no parasites can be found in peripheral blood smears from patients suffering from fulminant falciparum infection. This may be related to partial antimalarial treatment, or due to sequestration of parasitized cells in vascular beds of different organ systems. The importance of starting empiric treatment in critically ill patients with an illness compatible with fulminant *P. falciparum* infection is obvious. Time is of essence in severe infections; a delay of 24 hours or even less spells the difference between life and death.

When treatment is delayed to a point in time when multiple organ systems are already dysfunctional, death can occur from progressive multiple organ failure even when specific therapy has eliminated parasites from the blood. There is therefore a point of no return in some patients even with the best critical care if specific therapy is offered late in the natural history of the disease.

Enzyme-linked immunosorbent assays (ELISA) and radioimmunoassays (RIA) can detect 0.0001% of parasitemia.[3] Recently developed probes using genomic or synthetic *P. falciparum* deoxyribonucleic acid (DNA) can detect as little as 0.01 mg of parasite DNA after just 1 week's exposure. These are basically for research and epidemiological surveys, and have no role in the management of acutely ill patients in ICUs of poor developing countries.

Laboratory investigations should always include blood glucose levels; they should also include laboratory tests which monitor the function of different organ systems of the body. Fluid, electrolyte and acid-base studies are important, as derangement of these parameters can be easily rectified.

Though leucopenia or a normal leucocyte count is the rule in fulminant falciparum infections, a mild neutrophilic leucocytosis does not exclude the diagnosis. Blood cultures for bacteremia should always be done in the presence of a neutrophilic leucocytosis.

Differential Diagnosis

Mistakes in diagnosis are frequent, and would probably include consideration of a large cross-section of emergency medicine. Fever, hepatosplenomegaly, jaundice with increased liver enzymes and an increased bleeding tendency can also occur in dengue, leptospirosis, typhoid and other hemorrhagic fevers. Typhoid though is not generally accompanied by purpura or an increased bleeding tendency. Heat stroke in the hot summer months in North India bears a close resemblance to cerebral malaria. Acute pyogenic meningitis can be easily differentiated by a cerebrospinal fluid (CSF) examination. The association of fever with convulsions is also observed in encephalitides, metabolic encephalopathy, status epilepticus, cerebrovascular accidents, poisonings and eclampsia.

The algid form may be mistaken for heat exhaustion or food poisoning. Nonspecific abdominal pain in fulminant infections has convincingly mimicked an acute abdomen. Icterus with fever may be mistaken for viral hepatitis. The presence of fever with multiple organ system dysfunction may be mistaken for Gram-negative sepsis. Fulminant *P. falciparum* infection in fact constitutes protozoal sepsis.

Fulminant falciparum infection presenting with or soon evolving into disseminated intravascular coagulation (DIC) can be mistaken for overwhelming bacterial sepsis or DIC due to other causes. Fever with shock (algid malaria) may mimic dengue, septic shock, cardiogenic shock, hypovolemic shock or shock caused by an intra-abdominal catastrophe.

In fact fulminant falciparum infection may mimic almost every medical emergency that finds its way into a critical care unit. The differential diagnosis of severe fulminant *P. falciparum* infection is listed in Table 1.

MANAGEMENT[1,11]

Patients with fulminant *P. falciparum* infection, and, in particular, with cerebral malaria, require prompt admission to the ICU. A central venous line should be quickly secured

Table 1: Differential diagnosis of severe fulminant *P. falciparum* infection

Clinical presentation of severe (fulminant) P. falciparum infection	*Differential diagnosis*
Fever, splenomegaly, jaundice with increased liver enzymes with or without purpura or bleeding tendency	Dengue, leptospirosis, salmonella infection
High fever or hyperpyrexia with mental obtundation	Heat fever in hot summer months Pyogenic meningitis
Fever with convulsions	Encephalitides, metabolic encephalopathy, status epilepticus, cerebrovascular accident, poisoning and eclampsia
Algid form	Heat exhaustion and food poisoning
Nonspecific severe abdominal pain	Acute abdomen
Fever with jaundice	Viral hepatitis
Fever with multiorgan dysfunction	Bacterial sepsis
Fever with pulmonary edema [acute respiratory distress syndrome (ARDS)]	Leptospirosis, dengue, salmonella infection, other causes of noncardiogenic pulmonary edema
Fever, hemolysis with hemoglobinuria	Hemolytic uremic syndrome—other causes of hemolysis and hemoglobinuria
Fever with shock	Dengue, cardiogenic shock, hypovolemic shock, shock due to an intra-abdominal catastrophe
Fever with disseminated intravascular coagulation (DIC)	Fulminant dengue, DIC due to bacterial sepsis; other causes of DIC

and all vital signs carefully monitored. If a clinical diagnosis is made, a careful search for malarial parasites by an experienced pathologist in thin and thick peripheral smears is almost always rewarding. Blood cultures, blood glucose, serum electrolytes and arterial pH and blood gas analysis are done. If in an area endemic for malarial infection, early investigations reveal no clear cause for a clinical picture strongly suggestive of cerebral malaria, specific treatment against *P. falciparum* infection should be promptly started and continued, unless another definite cause for the illness is established.

Specific Therapy[1]

Many patients with *P. falciparum* malaria in India, Africa, Southeast Asia and in other endemic areas of the world are resistant to chloroquine. The drug should therefore not be used in *P. falciparum* infection, more so in fulminant falciparum infection where urgency of appropriate treatment is vital for survival. Specific antimalarial chemotherapy detailed below should be given not only to those with severe proven falciparum infection, but also to those living in endemic areas where a critical illness is compatible with or indistinguishable from fulminant falciparum infection.

The drug of choice at present is artesunate, treatment being initiated by an intravenous (IV) bolus injection. Artesunate given parenterally has replaced quinine as the drug of choice both in patients with severe falciparum infection and in patients who are vomiting and unable to retain swallowed tablets.[12,13]

The dose of artesunate is 2.4 mg/kg IV (loading dose) on the 1st day, followed by 1.2 mg/kg IV daily for a minimum of 3 days and preferably 5 days or until the patient can take oral therapy. The drug can also be given in the above dosage by intramuscular (IM) injection, though the IV mode of administration is clearly preferred.

Artemether®by IM injection or quinine by intermittent or continuous IV infusion is less effective when compared to artesunate.

The recommended dose of Artemether® is 3.2 mg/kg IM as the loading dose followed by 1.6 mg/kg IM daily for a minimum of 3 days and preferably 5 days or even more days until the patient can take oral therapy.

The recommended dose of quinine is 20 mg salt/kg loading dose diluted in 10 mL isotonic saline/kg given IV over 4 hours, followed by 8 hours after start of the loading dose with 10 mg/kg over 2 hours every 12 hours until the patient can swallow.

The 7-day course should be completed with quinine tablets 10 mg slat/kg (maximum 600 mg) every 8–12 hours.

In patients admitted to the ICU where they are under close observation the recommended dose of quinine is 7 mg of the salt/kg IV as the loading dose by an infusion pump over 30 minutes, followed immediately with 10 mg salt/kg IV over 2 hours every 12 hours till the patients can swallow.

Quinidine can be used in place of quinine but dangerous arrhythmias can occur. We have never used quinidine even when it was available in India. At present the drug is not available either for oral or IV use.

If facilities for giving IV injection or infusion are not available either artesunate or Artemether® can be given intramuscularly, the dose of each being the same as stated above.

Quinine can also be given intramuscularly if IV infusion for some reason is not possible. The dose is 20 mg/kg diluted

to 60–100 mg/mL as the loading dose, followed by 10 mg salt/kg every 8 hours until the patient can swallow. Quinine when given intramuscularly can cause severe tissue necrosis leading at times to abscess formation. Tetanus is a known complication following IM quinine. It can be avoided by scrupulous sterile precautions.

If it is not possible to give drugs by IV infusion or by IM injection, or if it takes time for parenteral therapy to be arranged, artemisinin can be used in the suppository form—40 mg/kg loading dose as an intrarectal suppository, followed by 20 mg/kg at 4, 24, 48 and 72 hours, followed by an oral anti-malarial drug.

Outside large cities, particularly in smaller districts of India, artesunate is often unavailable, the only drug for systemic parenteral use being quinine. It is therefore important to be aware of the side effects and toxic effects of quinine.

Hypoglycemia is the most important complication of quinine therapy. Quinine also produces cinchonism, characterized by tinnitus, impaired hearing, blurred vision, tremors and giddiness. The most dangerous side effect of quinine, particularly when used intravenously, is the occurrence of arrhythmias—in particular, ventricular tachycardia. A prolonged QTc interval is a warning of the possible occurrence of such arrhythmias. ECG monitoring is therefore very necessary in critically ill patients. Rarely hemolysis, thrombocytopenia and granulomatous hepatitis are observed. High blood concentrations can cause deafness; blindness and CNS depression, are very rarely seen in patients treated for malaria. In patients who are G6PD deficient, quinine can cause severe hemolysis.

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FEATURES OF NOTE IN PARENTERAL THERAPY OF SEVERE FALCIPARUM INFECTION

1. The malarial parasite continues to outwit human ingenuity. Drug resistance remains an ever worrying problem. There is documentation of in vitro resistance of the *P. falciparum* parasite to artemisinin with delayed clearance of the parasite in Pailin, western Cambodia and possibly in neighboring countries.
2. The use of anti-malarial drugs is poorly controlled; availability of drugs in areas of the world where the disease is highly endemic is uncertain.
3. Fake drugs continue to penetrate the markets of Asia and Africa.
4. It is not sufficiently realized that since most deaths with falciparum infection occur within 4 days of starting therapy it is vital to achieve parricidal levels of the parenteral drug used as quickly as possible. As in severe sepsis from other causes "time" is crucial if patients are to be salvaged.
5. In fulminant infection, there are some who prefer to use parenteral *artemisinin and quinine*. There is no evidence that the use of both is synergistic and is better than the use of either one or the other.

Table 2: A parenteral chemotherapy schedule for severe falciparum infection

Drug	*Dose*
Artesunate	2.4 mg/kg IV (loading dose) on the 1st day, followed by 1.2 mg/kg IV daily for a minimum of 3 days and preferably 5 days or until the patient can take oral therapy. The drug can also be given in the above dosage by IM injection
	OR
Quinine	20 mg salt/kg loading dose diluted in 10 mL isotonic saline/kg given IV over 4 hours, followed by 8 hours after start of the loading dose with 10 mg/kg over 2 hours every 12 hours until the patient can swallow. Later 600 mg tds orally for 7 days
	OR
Artemether®	3.2 mg/kg IM as the loading dose followed by 1.6 mg/kg IM daily for a minimum of 3 days and preferably 5 days or even more days until the patient can take oral therapy

6. In the treatment of falciparum malaria which is not severe or fulminant, artemisinin-based combined therapy (ACT) has been advocated to prevent resistance. ACT consists of the use of artemisinin derivatives combined with drugs such as mefloquine, amodiaquine or pyrimethamine—sulphonamide. The WHO (2006) now recommends that combination therapy replaces monotherapy in the treatment of uncomplicated *P. falciparum* infection.[1] This has proved effective except in Southeast Asia (Cambodia, Thailand and Burma) where resistance to artemisinin has been reported.

The drugs combined with artemisinin depend on the resistance of local strains of *P. falciparum*. In Southeast Asia lumefantrine or mefloquine may be added; in Africa lumefantrine, amodiaquine or pyrimethamine-sulfonamide may be added. The drugs and their dosage commonly used in severe falciparum infection are listed in Tables 2 and 3.

CRITICAL CARE[14,15]

Overall critical care is of vital importance. The central venous pressure is best maintained around 5–7 mm Hg, as overhydration carries the risk of inducing ARDS in these patients. Hyperpyrexia must be controlled with tepid sponging, cooling blankets and paracetamol. Fluid, electrolyte and acid-base balance must be meticulously maintained.[15] Intravenous dextrose is generally continued during quinine therapy to counter hypoglycemia.

In obtunded or comatose patients with cerebral malaria, it is important to protect the airway by elective intubation; every effort must be made to prevent aspiration pneumonia. Intravenous mannitol is used if there is an increase in intracranial pressure. Seizures are controlled by 20–40 mg diazepam given as a titrated infusion in 5% dextrose or by IV 2 to

Table 3: Chemotherapy for chloroquine sensitive P. falciparum or P. vivax, P. ovale, P. malariae, or when the patient cannot swallow

Drug	*Dose*
Chloroquine	The initial dose of 10 mg/kg should be administered over a period of not less than 8 hours, preferably by very slow intravenous infusion. Subsequent infusions of 5 mg/kg should be administered every 8 hours until a total dose of 25 mg/kg has been given
	OR
Quinine	20 mg/kg IV loading dose in 5% dextrose over 4 hours, followed by 10 mg/kg over 2–4 hours q8 h (maximum 1800 mg/d)—20 mg/kg IV loading dose in 5% dextrose over 4 hrs, followed by 10 mg/kg over 2–4 hrs q8h (maximum 1800 mg/d) until PO therapy can be started. Later 650 mg TDS × 7 days

4 mg lorazepam. Dilantin sodium may be given intravenously in addition. Delirious patients must be carefully restrained through good nursing care. A fall from the bed can precipitate a splenic rupture, a rare but recognized complication.

Ventilator support is always indicated in comatose patients particularly in the presence of seizures. It is also indicated in patients with ARDS or in severely tachypneic patients even when there is no evidence of acute lung injury.

Splenic Rupture

Sudden abdominal pain, often associated with pain over the left shoulder should arouse suspicion of a splenic rupture particularly if there has been possible trauma—as, for example, a fall from the bed. Hemodynamic instability or deterioration strengthens this suspicion. An ultrasonography (USG) of the abdomen or a computed tomography (CT) of the abdomen can confirm a splenic rupture with hemorrhage into the peritoneal cavity. Treatment depends on the extent of rupture and the clinical features. Conservative management with blood transfusions and careful observation in a critical care unit may be successful. Surgery may be imperative in difficult situations characterized by a large splenic tear causing hemodynamic deterioration.

Hypotension

Hypotension can be due to hypovolemia, blood loss, hemolysis, septic shock or hypoxia. Management consists of volume expansion with colloids, crystalloids and if necessary with packed cells. Inotropic and vasopressor support are invariably necessary. Suitable antibiotics are used against complicating bacterial sepsis. Proper arterial oxygenation and oxygen transport are important features of critical care.

Renal Failure

Renal failure should be addressed by correcting prerenal factors that can cause oliguria and azotemia. Use of hemofiltration or dialysis may be necessary till kidney function has sufficiently recovered.

Disseminated Intravascular Coagulopathy

Disseminated intravascular coagulopathy is a dreaded complication. It should be treated with IV vitamin K, infusions of fresh frozen plasma, cryoprecipitate, prothrombin complex and platelet infusions.

Support to all organ systems is necessary for survival in critically ill patients.

MANAGEMENT OF PREGNANT WOMEN WITH SEVERE FALCIPARUM INFECTION[1]

WHO (2006) has recommended artesunate and Artemether® in preference to quinine in the second and third trimesters of the pregnancy because they do not cause recurrent hypoglycemia. However, blood glucose must be checked daily in pregnant women whether or not they have been prescribed quinine. In the first trimester WHO recommends quinine in preference to artemisinin derivatives as the risk of hypoglycemia with quinine is lesser than the potential greater risk to the fetus following the use of artemisinin.

Induction of labor, cesarian section, accelerating the second stage of labor should receive prompt serious consideration in pregnant women with severe falciparum infection.

HYPERPARASITEMIA AND EXCHANGE BLOOD TRANSFUSION

Hyperparasitemia (>500,000/μL) or greater than 20% in nonimmune patients is believed to be associated with a high mortality. Exchange blood transfusion, hemopheresis and even plasmapheresis have been used with success in these circumstances, particularly when there is a poor response to specific chemotherapy. The above procedures would not only sharply reduce parasitemia, but also remove cytokines, other noxious mediators and restore RBC mass, platelets, clotting factors and albumin.

We have however never been advocates of exchange transfusions even before the introduction of artemisinins. Artemisinins now get rid of parasitemia very quickly, so that it is doubtful whether additional reduction of the parasitic load is of significant help.

MORTALITY[16]

In good units, severe *P. falciparum* infections should not carry an overall mortality greater than 20–25%. The mortality in our unit for just single organ failure is less than 10%. The mortality for two organs failure approximates 20%; it increases to 50% when three or more organs fail. Krishnan and Karnad[16] in an excellent study on 301 patients with severe *P. falciparum* infection observed a mortality of 48.8% with two or more organ failure. Even so, this is one tropical condition where multiple organ dysfunction and failure is not necessarily associated with as forbidding a mortality as that reported in western literature. We have observed that

in patients seeking early admission, prompt treatment with an artemisinin or quinine and good critical care can lead to survival even when SOFA scores are as high as 12–15 [see Chapter Multiple Organ Dysfunction Syndrome (MODS)].

Mortality is frequently but not necessarily related to the degree of parasitemia; yet, a parasite count greater than 500,000 mL is believed to carry a 50% mortality. Severe ARDS carries a bad prognosis, as does complicating bacterial infection. Fulminant disseminated intravascular coagulopathy in association with severe ARDS is invariably fatal. Persistent lactic acid acidosis, profound persistent hypotension are associated with a high mortality.

ACUTE VIVAX, OVALE, MALARIAE MALARIA[1]

Acute vivax malaria is associated with symptoms of fever with severe rigors followed by drenching sweats; but the mortality is very low. Certain forms of vivax malaria pose life-threatening emergencies. These are briefly mentioned below—

- Vivax malaria can lead at times to severe anemia which may be life-threatening in debilated individuals.
- Splenic rupture is more common in vivax infection rather than in falciparum infection. It can occur following even minor trauma, or spontaneously following sudden rapid enlargement of the spleen.
- Acute respiratory distress syndrome is now a well-recognized complication of vivax infection and carries a significant mortality, particularly if not correctly treated.
- Cerebral vivax malaria has occasionally been reported though some of these patients may have an associated undetected falciparum infection.

P. ovale malaria causes negligible mortality but *P. malariae* can lead to chronic morbidity and mortality by causing nephrotic syndrome and the tropical splenomegaly syndrome. Cerebral malariae malaria has been reported; it is rare and the possibility of an associated *P. falciparum* infection cannot always be excluded.

Treatment of *P. Vivax, P. Ovale, P. Malariae* Malaria

Chloroquine is the treatment of choice. Severe infection will require parenteral treatment. Chloroquine resistant *P. vivax* infection is treated by increasing doses of oral chloroquine. The oral dose of chloroquine is 600 mg base on the 1st and 2nd day; 300 mg on the 3rd day.

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TETANUS

INTRODUCTION

Tetanus is a killer disease afflicting the poor underprivileged people of the developing third world countries. It is caused by contamination of a wound by *Clostridium tetani (C. tetani)*, which is a Gram-positive, anaerobic and spore-forming organism. The spores gain entry through any wound; only the wound may be so minor that it may escape notice. Patients with tetanus require critical care, and in the larger cities of India are admitted either to special tetanus wards (equipped as ICUs) or to general medical ICUs. The fulminant form of the disease is a challenge to all that critical care medicine stands for. Successful management necessitates the application of every basic tenet of critical medical and nursing care.

The mortality of neonatal tetanus worldwide is close to 1,000,000 deaths each year. In our country, as also in other third world countries, the disease chiefly afflicts the younger age group between 17–30 years. In the west, the disease is extremely rare, and is nearly extinct in some countries. When it does occur, it is commoner in people older than 50 years, in whom the effects of immunization have worn off, in the non-immunized, in the impoverished and in drug addicts.

Tetanus is a disease of wounds; any wound however trivial can result in the disease. In fact 20% of patients have no evidence of a wound, nor do they give a history of injury. Contamination of wounds by manure, garden soil, or rusty implements is particularly dangerous. In our part of the world, tetanus can complicate burns, middle ear infections, septic abortions, childbirth and surgery. Tetanus neonatorum is most often due to non-sterile obstetric techniques, and to the dreadful habit of application of infected material such as cowdung to the umbilical stump.

PATHOPHYSIOLOGY[1,2]

Under anaerobic conditions, tetanus bacilli within a wound produce a neurotoxin called tetanospasmin. This toxin spreads to underlying muscles and is bound to receptors containing gangliosides on the neuronal membranes of the presynaptic nerve terminals. It is then internalized and transported intra-axonally and retrogradely within the peripheral nerves to the motor horn cells of the segment of the cord supplying the muscles. The toxin also invariably enters the bloodstream. It does not cross the blood-brain barrier, but via the blood it reaches and is bound to numerous nerve terminals in muscles throughout the body. It is then transported intra-axonally and retrogradely along numerous peripheral nerves to reach the alpha motor neurons of the whole spinal cord and brainstem. It also reaches the sympathetic ganglia, the lateral horns of the spinal cord and the parasympathetic centers. After reaching the cell bodies in the spinal cord and the brainstem, the toxin crosses the presynaptic cleft, and is bound to receptors on presynaptic nerve terminals of inhibitory interneurons (Fig. 2). Tetanus toxin now blocks the release of inhibitory neurotransmitters (chiefly glycine and gamma aminobutyric acid) from nerve terminals of inhibitory neurons.

The motor and autonomic neurons are now devoid of inhibitory control which lead to an uncontrolled, disinhibited efferent discharge from motor neurons of the spinal cord and brainstem to both agonist and antagonist muscles, causing muscle rigidity and reflex muscle spasms that characterize the generalized forms of the disease. Disinhibited autonomic discharge leads to excessive sympathetic activity with increased catecholamine levels in the blood, as also to excessive parasympathetic activity. Medullary and other centers in the brainstem and the hypothalamus may also be affected by tetanus toxin. The direct action of tetanus toxin on organ systems has not been proven, but remains a distinct possibility.

ALTERED HEMODYNAMICS[1-3]

Severe tetanus is characterized by a hypermetabolic, hyperdynamic, hyperkinetic circulatory state with tachycardia and an increased cardiac output. The details of the hemodynamics in patients with severe uncomplicated tetanus are illustrated in Figure 3.

Autonomic nervous system disturbances can profoundly affect the circulatory state. Autonomic storms described under complications are characterized by a paroxysmal seizure-like discharge causing marked tachycardia and hypertension. A cessation of this discharge leads to bradycardia and hypotension. Increased parasympathetic activity is as integral a feature of tetanus as sympathetic overactivity. The imbalance between the sympathetic and parasympathetic systems, with fluctuations in tone and activity, leads to marked cardiovascular instability.

Our studies on tetanus suggest that though the myocardium responds well to volume load, the response is not as good as in control subjects.[1-3] Myocardial function is thus suspect; whether this is related to tetanus toxin per se, or is related to factors common to any critical illness, is uncertain. Our experience also suggests that tetanus toxin may have a direct depressant effect on infranodal conduction causing infranodal block and arrest.[1-3]

CLINICAL FEATURES AND DIAGNOSIS

Generalized Tetanus

The two basic clinical features of tetanus are increased muscle tone and spasms. Fulminant tetanus is also invariably associated with autonomic disturbances.

Rigidity or increased muscle tone generally first involves the masseters, resulting in difficulty in opening the mouth—

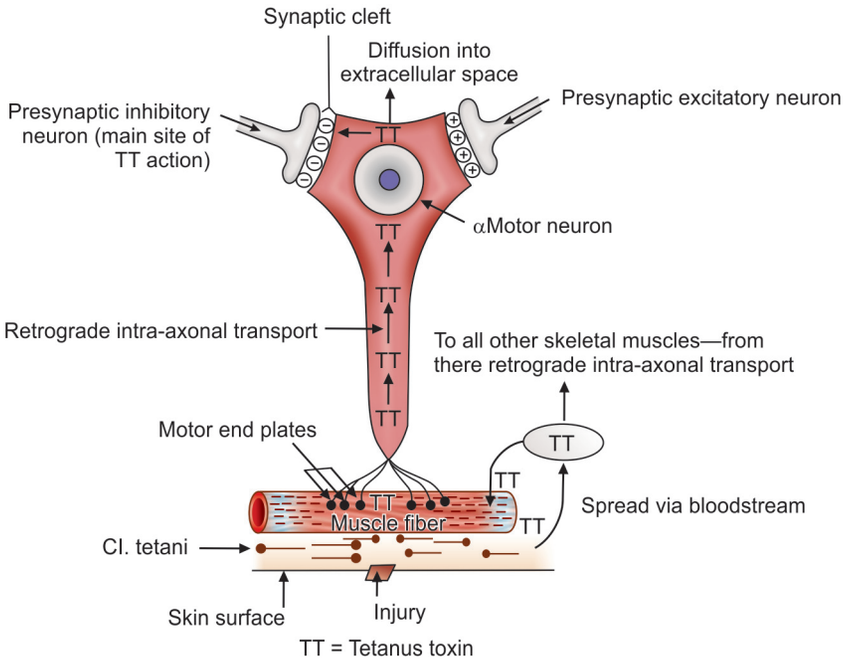

Fig. 2: Retrograde intra-axonal transport and main site of action of tetanus toxin (TT) in the central nervous system. The toxin ascends retrogradely along axons of the peripheral nerves to reach the alpha motor neuron cell bodies. It then crosses the synaptic cleft to reach the terminals of the presynaptic inhibitory neurons where it exerts its main action by binding to receptors on the presynaptic membrane. Tetanus toxin also acts on the neuromuscular junctions of the peripheral nerves, as well as on the presynaptic excitatory neurons. The clinical picture of tetanus is however largely related to its main site of action

Source: Reproduced with permission from Udwadia FE. Tetanus. Mumbai: Oxford University Press; 1994.

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trismus or lockjaw. It soon involves the muscles of the face giving rise to the typical tetanus facies, with a "risus sardonicus". The muscles of the neck, trunk, back and extremities are all involved. The limbs are ramrod stiff, the abdomen may show board-like rigidity, and increased tone in the muscles of the neck and back can cause opisthotonos with retraction of the head, closely simulating meningitis.

Muscle spasms or seizures form the hallmark of severe tetanus. Seizures are easily induced by touch, noise or emotional stimuli. They often occur spontaneously, and vary in frequency and severity. Spontaneous seizures in the very severe forms of the disease occur at very brief intervals, so that the patient often is in a perpetually convulsed state. Protracted spasms often involve the pharynx, rendering swallowing impossible. Laryngeal spasms can lead to asphyxia. Powerful frequent spasms of the respiratory muscles render breathing impossible, so that the patient becomes hypoxic and even cyanosed.

Severe tetanus is a painful, febrile disease associated with tachycardia, sweating and an unstable cardiovascular system. Unless expertly managed, the patient succumbs to respiratory complications, circulatory failure, cardiac arrest, or to complications causing multiple organ failure.

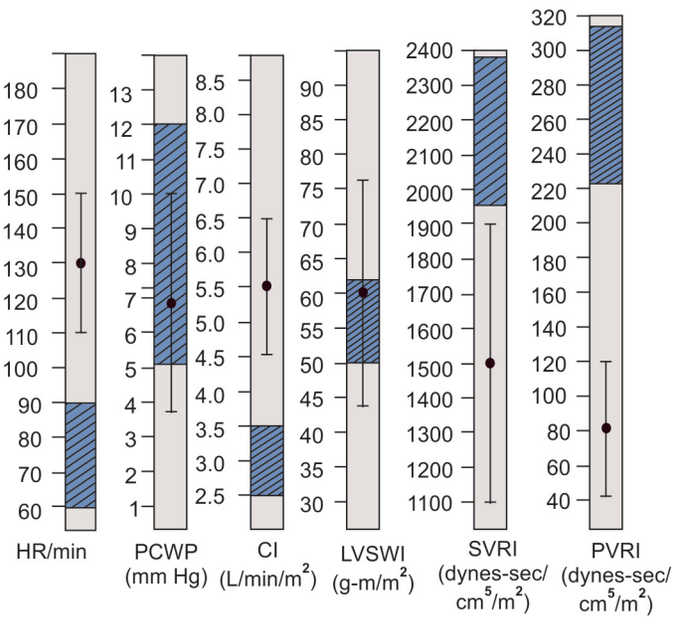

Fig. 3: Hemodynamic observations in 19 patients with severe uncomplicated tetanus (I = mean + SD). Shaded areas show range of normal values. *Abbreviations*: HR, heart rate; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; LVSWI, left ventricular stroke work index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index.

Autonomic Nervous System Disturbances

These are intrinsic to severe tetanus. Tachycardia (ranging 150–180/minute) persisting for days on end, drenching sweats, frequent elevations in systolic and diastolic blood pressure, increased salivary and tracheobronchial secretions, and evidence of increased vagal tone and activity are the usual features pointing to autonomic disturbances in severe tetanus.

Grading the Severity of Tetanus

This is not just an academic exercise; it helps in both the prognosis and the management of the problem. The criteria described below are arbitrary, but have been used by us over many years, and have stood the test of time.

Grade I (Mild)

Mild to moderate trismus; general spasticity; no respiratory embarrassment; no spasms; little or no dysphagia.

Grade II (Moderate)

Moderate trismus; well-marked rigidity; mild to moderate, but short-lasting spasms; moderate respiratory embarrassment with tachypnea greater than 30–35/minute; mild dysphagia.

Grade III (Severe)

Severe trismus; generalized spasticity; reflex and often spontaneous prolonged spasms; respiratory embarrassment with tachypnea greater than 40/minute; apneic spells; severe dysphagia; tachycardia usually greater than 120/minute; a steady moderate increase in autonomic nervous system activity.

Grade IV (Very Severe)

Features of Grade III plus violent autonomic disturbances often resulting in what may be aptly termed "autonomic storms" involving the cardiovascular system. These include episodes of severe hypertension and tachycardia alternating with relative hypotension and bradycardia, or severe persistent hypertension (diastolic pressure >110 mm Hg), or severe persistent hypotension (systolic pressure <90 mm Hg).

Cephalic Tetanus[1]

This occurs after wounds to the face or head and is typified by unilateral facial paralysis, trismus and facial stiffness of the unparalyzed side. Pharyngeal spasms causing dysphagia and frequent laryngeal spasms are generally present. Rarely, facial palsy is bilateral. Occasionally there is also paresis of the glossopharyngeal, vagal and rarely the oculomotor nerves. Cephalic tetanus often graduates to generalized tetanus.

Tetanus Neonatorum[1]

Even in the best of units this has a high mortality. The earliest symptom is a difficulty in suckling and swallowing due to stiffness of the masseters and the muscles of the pharynx. Stiffness extends to the face causing the classic tetanus facies. Skeletal muscle stiffness produces flexion at the elbows with the fists clenched and drawn to the thorax, extension of the knees with plantar flexion at the ankles and toes. There is retraction of the head with marked opisthotonos. Muscle spasms render breathing difficult. Autonomic disturbances occur and death results from cardiorespiratory failure.

Local Tetanus

Rarely tetanus is confined to a group of muscles adjacent to a wound, or confined to one limb.

NATURAL HISTORY

The incubation period of tetanus averages 7–10 days, but may range from 2 days to 2 months. The shorter the incubation period, the more severe the disease.

The period of onset is the time interval between the first symptom and the occurrence of muscle spasms or seizures, and it ranges from 1–7 days. The shorter the period of onset, the more severe the disease. The period of onset is a more reliable prognostic guide than the incubation period. The disease increases to its maximum intensity over a period of 7–10 days, then plateaus over the next 1–2 weeks, and then gradually declines over the next 2 weeks. The natural history of the disease is punctuated by numerous complications which have been briefly outlined later. Tetanus is a severely catabolic disease, with the patient remaining in a hypermetabolic state for 3–4 weeks. Significant weight loss is observed even in those who recover, and even when every aspect of nutrition is assiduously cared for.

COMPLICATIONS[1]

The natural history and management of moderate and, in particular, severe tetanus are bedevilled by numerous complications. As mentioned at the outset, any or every organ system can be involved. Respiratory and cardiovascular complications and those involving the autonomic system are inherent to the disease. Others are related to the prolonged management of critically ill individuals who have been paralyzed by curare-like drugs, and maintained on ventilator support for periods extending from 4–6 weeks.

Respiratory Complications[1,4]

These include atelectasis, aspiration pneumonia and bronchopneumonia. Infection is generally due to Gram-negative organisms, chiefly *Klebsiella* and the *Pseudomonas* species. Prolonged laryngeal spasm can produce death from asphyxia. Episodes of acute respiratory distress with tachypnea occur in both moderate and severe tetanus, and are probably related to release of inhibitory control over the respiratory center, induced by the tetanus toxin. Unrelenting continuous spasms render breathing impossible, and unless correctly managed, produce death from acute hypoxia. The adult respiratory distress syndrome is now increasingly

observed—it is chiefly due to iatrogenic sepsis, but can be due to tetanus per se. Complications related to tracheostomy and to prolonged ventilator support (chiefly pneumothorax and nosocomial pulmonary infections) are also observed.

Autonomic Cardiovascular Complications[1,3]

Marked tachycardia, as high as 180/minute has already been commented upon. Severe hypotension, labile hypertension, or persistent severe hypertension are all observed. Hypertensive patients are almost always extremely sensitive to beta-blockers. Severe peripheral vasoconstriction with a shock-like state resulting in rapid death is observed in a few fulminant cases. Autonomic storms are characterized by episodes of sudden severe tachycardia with severe hypertension (BP = 180–220/110–130 mm Hg), alternating within minutes with bradycardia (50–60/minute) and a fall in systolic blood pressure to less than 100 mm Hg. Marked cardiovascular instability results in, and is the forerunner of cardiac arrest and sudden death.

Increased vagal tone is invariably present and is manifested by increased tracheobronchial secretions, by sudden severe bradycardia and hypotension, and even arrest during suctioning of the trachea through the tracheostomy tube.

Cardiac arrhythmias are frequent and include supraventricular tachycardias, ventricular extrasystoles, junctional rhythms and short spontaneously reverting bursts of ventricular tachycardia.

Sudden hyperthermia (rectal temperature >41°C) can occur and result in cardiovascular collapse and death. Hypothermia may also be rarely observed. Sudden fluctuations in temperature are probably related to hypothalamic disturbance.

Sudden Death[1,4]

Sudden death remains the most dreaded complication of tetanus. In our experience, it constitutes the commonest cause of death in patients managed in well-equipped and well-staffed ICUs. Sudden death is related to the following factors—

- Marked cardiovascular instability due to fluctuating sympathetic tone.
- Excessive vagal tone causing reflexly induced bradycardia, hypotension and cardiac arrest.
- Hypoxia due to unremitting seizures or to prolonged laryngeal spasms.
- Hyperpyrexia, often unsuspected and sudden, causing cardiovascular collapse and death.
- Impaired infranodal conduction, probably related to the tetanus toxin per se.
- Massive pulmonary embolism.
- An unrecognized iatrogenic complication, as for example, tension pneumothorax.
- No obvious reason.

Multiple Organ Dysfunctions (MOD)

MOD is frequent in severe fulminant tetanus; it was observed in 22% of our cases. The system most frequently involved is of course the respiratory system, followed by the cardiovascular system, the GI system, the liver and the kidneys. Changes can also occur in the hematopoietic system. Hypotension with systolic blood pressure less than 70 mm Hg necessitating inotropic support may persist for days. GI dysfunction is evinced by ileus and massive bleeds. A rise in the liver enzymes to well above 100 IU, and of serum bilirubin up to 5 mg/dL is frequent. Mild elevations in the prothrombin time to one and half times the control value are also observed. Renal insufficiency is characterized by a rise in serum creatinine up to 3 mg/dL. Rarely acute renal failure requiring dialysis is observed. It is indeed remarkable and noteworthy that multiple organ dysfunction, when not induced by obvious sepsis, does not carry the grim prognosis reported in western literature, and recovery ensues provided excellent care is available.

Other Complications

These are chiefly iatrogenic and related to prolonged ventilator support in critically ill patients. These include sepsis, GI complications (GI bleeds, diarrhea, ileus), renal dysfunction, fluid and electrolyte disturbances, compression fractures of vertebrae, anemia and hypoproteinemia.

Miscellaneous complications include peripheral neuropathy, infected bed sores, thrombophlebitis, corneal ulcers and deep vein thrombosis in the lower limbs; this can result in death due to pulmonary embolism.

A list of respiratory, cardiovascular, autonomic and other complications observed in 233 patients at the JJ Hospital, and in 32 patients with severe tetanus at the Breach Candy Hospital is given in Tables 4 to 6.

DIAGNOSIS

The diagnosis is based on the clinical features; there is no laboratory test that can confirm tetanus. To the experienced eye, tetanus admits of no differential diagnosis. The tetanus facies is unmistakable. It occurs in no other disease, and it simply cannot be mimicked by even a trained malingerer for any length of time. Rarely, trismus may be an early feature of meningitis. A CSF examination clinches the diagnosis, as in tetanus the CSF is normal. Dystonic reactions produced by phenothiazines and metoclopramide bear no resemblance to tetanus, and can be easily distinguished from it. Cephalic tetanus may be mistaken for rabies because of dysphagia; however, hydrophobia is never present in tetanus.

MANAGEMENT[2]

Whenever possible, all patients with tetanus should be admitted to an ICU, or a specially equipped tetanus ward that functions as an ICU. Mild or Grade I tetanus poses no problems except when complicated by a serious or septic wound, which by itself can result in death. However, mild (Grade I) tetanus can graduate over a few days to moderate (Grade II) or even severe (Grades III and IV) tetanus. Even

Table 4: Respiratory complications in 265 patients with tetanus

	Number of patients
• Bronchopulmonary infections—	
– Pneumonia and bronchopneumonia	36
– Lung abscess	1
– Pyopneumothorax with bronchopleural fistula	1
• Significant pulmonary atelectasis	26
• Pneumothorax (iatrogenic)	5
• Pneumomediastinum	5
• Episodes of unexplained respiratory distress	29
• Adult respiratory distress syndrome	9
• Significant stridor	5
• Accidental disconnection of ventilator	1

Note: Atelectasis (segmental or subsegmental) is an invariable feature of severe tetanus. "Significant pulmonary atelectasis" includes only those patients where atelectasis persisted over a day in spite of repeated attempts to open up the involved segment or lobe.

Source: Reproduced with permission from Udwadia FE. Tetanus. Mumbai: Oxford University Press; 1994.

Table 5: Cardiovascular and autonomic complications in 233 patients at the JJ Hospital (JJH) and 32 patients at the Breach Candy Hospital (BCH), Mumbai

	JJH	*BCH*
• Sustained tachycardia (>150/min)	42	20
• Hypotension (systolic BP <90 mm Hg)	22	6
• Hypertension (moderate and severe)	20	11
• Episodic labile hypertension	12	8
• Sudden cardiac arrest with death	13	1
• Sudden cardiac arrest with successful resuscitation	6	3
• Severe sweating	30	26
• Severe vasoconstriction	15	1
• Hyperpyrexia (>42°C rectal)	12	11
• Cardiac arrhythmias—		
– Paroxysmal SVT	6	7
– Ventricular extrasystoles (frequent)	24	24
– Nodal rhythm	-	3
– Short runs of ventricular tachycardia	-	3
– Idioventricular rhythm	1	1
• Myocardial infarction	1	1
• Severe hypothermia	-	1

Note: The lower incidence of arrhythmias in the 233 patients at the JJ Hospital was due to imperfect monitoring conditions as compared to the Breach Candy Hospital, Mumbai.

Source: Udwadia FE. Tetanus. Mumbai: Oxford University Press; 1994.

mild cases, therefore, require close observation till the natural history of the disease is clearly established.

Table 6: Other systemic complications in 233 patients at the JJ Hospital (JJH) and 32 patients at the Breach Candy Hospital (BCH), Mumbai

	JJH	*BCH*
• Bacterial sepsis	5	7
• Multiple organ failure	-	7
• Septic shock with DIC	4	2
• Gastrointestinal—		
– GI bleed	56	4
– Paralytic ileus	38	3
– Diarrhea	24	3
• Renal failure	27	4
• Central nervous system (CNS) complications—		
– Obtunded mentation	10	4
– Peripheral neuropathy	4	2
• Metabolic and electrolyte disturbances	23	10
• Miscellaneous—		
– Keratitis	-	4
– Corneal perforation	-	1
– Fracture of vertebrae	2	2
– Urinary tract infection	13	12

Source: Udwadia FE. Tetanus. Mumbai: Oxford University Press; 1994.

Use of Antiserum

Immediately on admission to our unit the patient is given antiserum. Human tetanus immunoglobulin (HTIG) is superior to the equine antiserum as it does not produce a hypersensitivity reaction, and should be given in the dose of 3,000–5,000 international units intravenously or intramuscularly. However, in poor developing countries, equine antiserum is the only one generally available and 10,000 units are given intravenously after doing a skin sensitivity test. Fatal anaphylaxis can occur even in the absence of a positive skin test. Some workers infiltrate 3,000 units of the antitoxin locally around the wound, but this is of doubtful efficacy.

Antibiotics

Two mega units of crystalline penicillin are given IV for 8 days. Metronidazole, 500 mg IV 8 hourly for 5–7 days, has been currently recommended.

Management Strategies (Table 7)

Grade I or mild tetanus should be treated conservatively with the use of sedatives and muscle relaxants.

Grade II or moderate tetanus should have a tracheostomy done in addition to the use of sedatives and muscle relaxants.

Grade III and Grade IV or severe tetanus require sedation, tracheostomy, neuromuscular paralysis with curare-like drugs, and ventilator support till such time as the disease resolves and recovery ensues.

Table 7: Management strategies according to severity of tetanus

Mild or Grade I tetanus	Sedatives + Muscle relaxants
Moderate or Grade II tetanus	Sedatives + Muscle relaxants + Tracheostomy
Severe or Grades III and IV tetanus	Sedatives + Tracheostomy + Induced neuromuscular paralysis + Ventilator support

Source: Udwadia FE. Tetanus. Oxford University Press, Mumbai; 1994.

Use of Sedatives and Muscle Relaxants

This constitutes the traditional conservative management of tetanus. Even today, sedatives and muscle relaxants continue to be the only therapy available, even for severe cases, in many tetanus units in developing countries all over the world.

In good ICUs and in well-equipped tetanus wards, sedatives and muscle relaxants continue to form the basis of therapy for Grades I and II tetanus. We almost exclusively use diazepam as the drug of choice. The dosage in children and adults is 5–20 mg thrice daily and in neonates 2 mg thrice daily. In moderate (Grade II) tetanus, the drug is used as an IV infusion over 24 hours. We prefer not to exceed a dose of 80–100 mg IV over 24 hours, even in the presence of marked rigidity. Many units both in India and in the West and South America continue to use doses as high as 250–350 mg IV over 24 hours. In our wide experience with this disease over the years, we remain unconvinced that doses more than 80–100 mg/day, given over many days, confer any further benefit, or reduce the mortality associated with this disease. In fact, we feel that very high dosage schedules, as explained later, may do more harm than good, and particularly in the absence of ventilator support, always seriously depress respiration.

Other muscle relaxants in use include chlorpromazine, phenobarbitone, paraldehyde, mephenesin and meprobamate. The last two drugs are hardly ever used. A few units use chlorpromazine, or a combination of diazepam with chlorpromazine or phenobarbitone, or prefer to use all three drugs to help to achieve better control of severe rigidity. The dose of chlorpromazine is 50 mg intramuscularly, four times daily in adults, 25 mg in children and 12.5 mg in neonates. The dose of phenobarbitone is 200 mg in adults, 100 mg in children and 30 mg in neonates, given intramuscularly every 8–12 hours. Dantrolene is a relatively new muscle relaxant which has been used in tetanus; we however have no experience with this drug, but doubt that it has any significant additional advantage over diazepam.

Baclofen, a centrally acting muscle relaxant, has been used intrathecally by some workers, with satisfying results.[5,6] It has no special advantage[7] and, in our opinion, its use is not practical for poor third world countries.

Sedatives and muscle relaxants are of symptomatic use. The ideal sedative and muscle relaxant schedule for each patient should be so tailored as to ensure sedation, muscle relaxation and sleep, but should yet allow the patient to be aroused to obey commands. A practical, objective guide to the degree of muscle relaxation desired in moderately severe tetanus is the tone of the abdominal muscles which should feel relaxed and much less stiff on palpation.

Laryngeal spasm should be countered by an IV injection of 10–20 mg of diazepam, or 50 mg chlorpromazine, or by IV succinylcholine.

Tracheostomy

We consider this necessary even for Grade II or moderate tetanus and absolutely mandatory for Grades III and IV tetanus. In Grade II tetanus, an important cause of death, even in intensive care settings, is sudden, prolonged laryngeal spasm, which causes death by asphyxia. This is easily preventable by doing a tracheostomy. Inability of patients with moderately severe tetanus to swallow well, combined with the use of heavier sedation, are also indications for an elective tracheostomy.

Induced Paralysis with Ventilator Support

Severe tetanus should not be managed conservatively, solely with the use of sedatives and muscle relaxants. Conservative management in these patients carries an appallingly high mortality. These patients not only require an elective tracheostomy, but also need to be paralyzed by neuroparalytic agents and kept on ventilator support. Pancuronium is the neuroparalytic agent generally available in poor countries. Pancuronium 2–4 mg is given IV, and the dose is so titrated for each patient, that the neuromuscular paralysis achieved allows for efficient ventilator support. This is checked by serial measurements of arterial pH and arterial blood gases. The PaO_2 should be maintained greater than 70 mm Hg, and the $PaCO_2$ between 35–40 mm Hg. The initial requirement of the neuroparalytic drug may be as frequent as half to 1 hourly. With time the requirement falls to 2 hourly, and later still to even 6–8 hourly schedules. We prefer to use bolus injections in the manner stated above (as in our opinion these are better tolerated) rather than using a continuous IV infusion of the drug. Newer neuroparalytic drugs include vecuronium used in the dose of 6–8 mg/hour and atracurium (loading dose 0.23 mg/kg followed by an infusion of 5 µg/kg per minute).[8] The high cost of these two drugs however precludes their use in poor developing countries where tetanus is still rampant.

The average period of ventilator support in severe tetanus in our experience varies from 10 days to 6 weeks. Once spasms abate, pancuronium is stopped; ventilator support is however continued till the patient is deemed fit to be weaned. Premature weaning in the presence of excessively stiff chest muscles is unwise, and leads to problems necessitating reintroduction of ventilator support. The tracheostomy tube is removed only when the patient can cough well, swallow satisfactorily, and can handle his upper respiratory secretions without difficulty.

Treatment of Autonomic Circulatory Disturbances

A number of drugs have been used to treat autonomic storms producing severe cardiovascular instability in fulminant tetanus. These include beta-blockers,[9] heavy sedation,[10] IV morphine sulfate,[11] IV clonidine[12] and IV infusions of

magnesium sulfate.[13] However, these drugs do not alter the high mortality in fulminant disease. Our studies on the hemodynamics of severe tetanus have convinced us that it is best to rely on efficient cardiorespiratory support, and to avoid drugs that strongly depress the central or autonomic nervous systems. Hypotensive spells are treated with a volume load, and if this is inadvisable or ineffective, we use a titrated dose of dopamine sufficient to raise the systolic blood pressure just above 100 mm Hg. Hypertensive spells with systolic blood pressure greater than 200 mm Hg or a diastolic blood pressure greater than 110 mm Hg are best treated with 5–10 mg of oral propranolol, the dose being titrated to achieve an effective control over the heart rate and the blood pressure, or sublingual nifedipine (5 mg), or a combination of the above two. The use of IV beta-blockers is best avoided as these patients are extremely sensitive to these drugs, particularly when used intravenously. Bradyrhythms below 50/minute are treated with IV atropine, and severe sinus tachyrhythms greater than 170–180/minute with verapamil 40 mg twice or thrice daily. In patients with a shock-like state with increased SVR and a reduced CI, 2–5 mg morphine given intravenously helps sometimes in effectively reducing the SVR, and improving the cardiac output and tissue perfusion. The dose again needs to be titrated as per the patient's response, and the dose may be repeated, if necessary. Patients with the above-mentioned hemodynamic abnormality, who do not respond to morphine, should be given a trial with a slow titrated infusion of sodium nitroprusside, so as to reduce the SVR. We invariably combine this with simultaneous dopamine inotropic support.

Severe tetanus is often associated with hypotension (systolic blood pressure <70–80 mm Hg). Unless the intravascular volume is definitely depleted, it is unwise to use large fluid challenges to increase the arterial blood pressure. The compliance of both the systemic and pulmonary vasculature is markedly increased in these patients, and volume replacements are literally swallowed up in the compliant vessels, or tend to produce noncardiogenic pulmonary edema and ARDS. The CI may still be markedly raised in the presence of a low arterial blood pressure. Even so, the use of dopamine inotropic support is advocated so as to maintain the systolic blood pressure in young individuals between 90–100 mm Hg, and in older patients close to 120 mm Hg. This ensures adequate oxygen transport and allows for an increased oxygen uptake by hypermetabolic tissues.

In our opinion, high doses of diazepam (150–300 mg/day IV) in severe tetanus are unwise, and may well contribute to a high mortality. Such high doses by strongly depressing the autonomic and CNSs, may predispose to cardiac arrest during episodes of bradycardia and hypotension, or could well prevent successful resuscitation following cardiac arrest. We advocate only 30–50 mg/day of IV diazepam in patients who are paralyzed and on ventilator support.

The management principles enunciated and discussed above have resulted in a mortality as low as 6% in our ICU in patients with severe fulminant tetanus.

Box 3: Summary of the management protocol in tetanus

- Antiserum—Equine antitoxin 10,000 units IV after test dose. If available, 3,000–5,000 IU of human tetanus immunoglobulin (HTIG) preferred
- Antibiotics—Crystalline penicillin 2 mega units IV for 8 days + metronidazole 500 mg IV 8 hourly
- Care of the wound according to general surgical principles
- Sedatives and muscle relaxants—used for all grades of tetanus. The sedative most commonly used is diazepam, 20 mg 8 hourly IV, in adults. We do not exceed a dose of 100 mg/24 hours
- Tracheostomy—done in Grades II, III and IV tetanus
- Induced paralysis + ventilator support—used in Grades III and IV tetanus. Pancuronium 2–4 mg IV as and when required (to start with, every half to 1 hour)
- Treatment of autonomic circulatory disturbances—
  - Hypotensive spells treated with volume load, or if this is ineffective or inadvisable, a titrated dose of dopamine is used for inotropic support. Maintain BP around 100–120/80 mm Hg
  - Hypertensive spells treated with 5–10 mg oral propranolol, or 5 mg sublingual nifedipine, or a combination of both drugs. Avoid IV propranolol. Morphine 2–5 mg IV is used in patients with low CO and high SVR. Morphine in an IV infusion may also be used
  - Bradyrhythms less than 50/min treated with IV atropine
  - Sinus tachycardia greater than 180/min treated with verapamil 40 mg thrice a day
- Treatment of other complications
- Overall critical care and nursing
- Nutrition—maintain a caloric intake of 2,500–3,000 cals/day, with 75–100 g of proteins/day

Treatment of Other Complications

Prevention, prompt recognition and treatment of the numerous complications that can involve almost each and every system, is vital if mortality is to be reduced.

Critical Care and Nursing

No other illness makes greater demands on a critical care unit than severe fulminant tetanus. Critical care of the patient as a whole and expert nursing are of crucial importance. Special emphasis should be laid on meticulous care of the tracheostomy and on good physiotherapy. In addition to maintaining the arterial blood gases within the normal range, adequate oxygen transport must be ensured. Packed cells should be transfused to correct anemia; cardiac output is enhanced by inotropic support, if necessary.

Nutrition

Tetanus is a severely catabolic disease, and generally occurs in patients with a poor nutritional state. Good nutrition is

imperative for survival. A caloric intake between 2,500–3,000 calories/day, with at least 75–100 g of protein is given in the form of liquid or semiliquid food through the nasogastric tube.

A summary of the management protocol in tetanus has been tabulated in Box 3.

PREVENTION

Tetanus is a dreadful disease which is almost totally preventable by proper active immunization and proper care of wounds. An attack of tetanus does not confer immunity from another attack. Immunization with tetanus toxoid should begin during convalescence. Some prefer to administer the first dose of toxoid soon after admission to the ICU. It is fortunate that the overall incidence of tetanus has declined over the last 15 years, probably due to a more efficient immunization program.

MORTALITY

Mortality depends on the severity of tetanus. A short incubation period (<4 days) and a short period of onset (<2 days) signify severe disease and prognosticate a high mortality, often over 50%. Tetanus neonatorum carries a mortality of 60–80%. The overall mortality in tetanus, reported from different countries, ranges from 20% to 60%. In Mumbai till 10 years back, overall mortality in a large teaching hospital was 30%, and the mortality in fulminant tetanus was between 70% and 100%. This high mortality was due to a failure to grasp the principles of critical care and ventilator support. With the management strategies outlined above, the overall mortality in the same teaching hospital fell to 12%, and mortality in severe tetanus to 23%.[4] With better intensive care facilities, the mortality of severe tetanus has been brought down to around 6%.[3] These results amply justify our management strategies discussed above.

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ACUTE DISSEMINATED HEMATOGENOUS TUBERCULOSIS

GENERAL CONSIDERATIONS

The problem of acute disseminated hematogenous tuberculosis is of importance in critical care medicine in India, and in other developing countries. This is because of the wide prevalence of tuberculosis in poor countries, and the certain increase in incidence likely to occur with the spread of AIDS in these countries.[1] According to the WHO report (2009) on tuberculosis, the incidence of tuberculosis in India is 168/100,000 population per year.[2] The diagnosis of acute disseminated hematogenous tuberculosis is easy in a patient with known tuberculosis in the recent past. When the problem presents de novo, or when it occurs in immunocompromised patients who are extremely prone to both community acquired and opportunistic pathogens, the diagnosis can be extremely difficult.

CLINICAL FEATURES AND DIAGNOSIS (BOX 4)

Fever of unknown origin is the presenting feature. Clinical deterioration can occur over a period of months, but is observed in a matter of days in immunocompromised individuals.[3] Pulmonary lesions are invariably present, but can be easily missed. Miliary shadows may be undetectable on a portable chest X-ray, and the sputum examination may not be possible, as the patient either has no expectoration, or is too ill to expectorate. At times, the disease manifests with fever and bilateral diffuse shadows in both lungs on an X-ray of the chest. There may be little or no cough and there is generally no sputum. Tachypnea is an important feature; the clinical picture is that of ARDS with well-marked hypoxemic respiratory failure, necessitating intubation and mechanical ventilator support. The relation of these "shadows" within the lung to tubercle can only be proven by examination of the BAL fluid obtained through fiberoptic bronchoscopy. The BAL fluid shows acid-fast bacilli and a transbronchial biopsy often shows ceseating granulomas.

Box 4: Features suggestive of disseminated hematogenous tuberculosis

- Fever of unknown origin lasting over a few weeks, with sudden deterioration especially in immunocompromised patients
- Tachypnea
- Sputum scanty or absent
- Hypoxemic respiratory failure—ARDS
- Initially a hyperdynamic circulation as in sepsis, soon followed by a fall in cardiac output and shock
- Miliary or scattered shadows within the lung
- Diagnosis most often made by fiberoptic bronchoscopy
- AFB present in BAL fluid; caseating granulomas may be seen in transbronchial biopsies
- CT chest or abdomen may show evidence of lymphadenopathy
- Frequent evidence of liver cell dysfunction
- Multiple organ dysfunction indistinguishable from sepsis
- Recovery possible if diagnosed early and treated promptly

Over a varying period of time (15 days to 1 month), patients who are critically ill invariably develop dysfunction of multiple organs. The liver and the spleen may both be palpable, and liver functions are frequently deranged with a rise in serum bilirubin to well beyond 5 mg/dL, a significant increase in the transaminases, and a prothrombin time more than one and a half times the control value. A liver biopsy may show ceseating granulomas. Very ill individuals have a fall in systolic blood pressure below 90 mm Hg (often as low as 70 mm Hg), and require inotropic support. GI bleeds and ileus make maintenance of nutrition difficult. Anemia and hypoproteinemia are both invariably present; the former is due both to blood loss and to infection. The white blood cell (WBC) count may not be of much help. Normal counts, leucopenia, or a mild to moderate leucocytosis may be observed. The ESR however is invariably raised, and is in the region of 100 mm/hour by the Westergren method. There may however be exceptions to this rule, particularly in the early phase of the natural history of the disease.

The patient may be obtunded even when the CSF examination is normal, and even with no evidence of tuberculomas in the brain on a CT examination of the head. The clinical picture in the fully evolved disease is often indistinguishable from sepsis with multiple organ dysfunction.

The presentation with multiple shadows within the lung evolving into the ARDS with multiple organ dysfunction is generally observed in immunocompromised patients, including those on corticosteroids. Rarely, it may occur in immunocompetent individuals as well.

The diagnosis may be difficult and at times impossible to establish. Repeated blood cultures in the early phase of the illness for Gram-negative infections, and peripheral smears to exclude *P. falciparum* infection should be done. As has already been mentioned, a fiberoptic bronchoscopy with bronchoalveolar lavage and a transbronchial biopsy are, in our experience, probably the most useful investigations.[4] Acid-fast bacilli can be demonstrated in bronchial aspirates or grown on culture. Biopsies (including liver biopsy) may show ceseating granulomas. CT examination of the chest and abdomen may provide tell-tale clues by demonstrating the presence of enlarged necrotic glands. A CT of the head may unexpectedly reveal tuberculomas in the brain.[5] If the patient is not too ill and if the above investigations are negative, an open lung biopsy is of great help in the presence of pulmonary shadowing of undetermined etiology. Tuberculosis may manifest in the most bizarre fashion, particularly in countries where the disease is common. It should never be forgotten

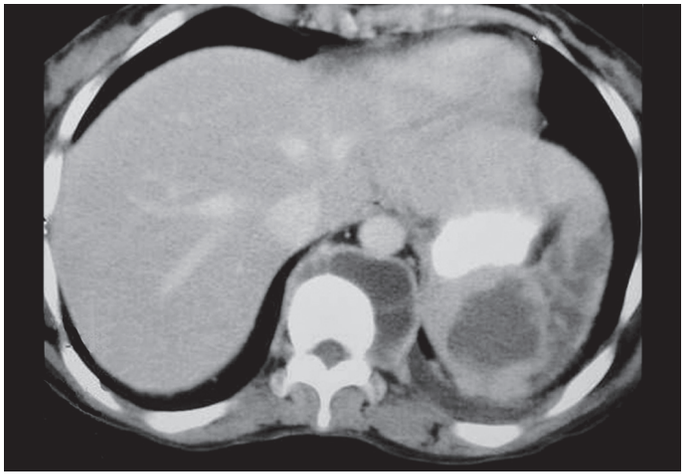

Fig. 4: Hematogenous disseminated TB—CT scan following contrast reveals focal hypodense lesions in the spleen as well as a preparavertebral abscess. There is splenic as well as vertebral involvement in this patient having disseminated hematogenous tuberculosis

as an important differential diagnosis in an acute, life-threatening obscure illness (Fig. 4).

MANAGEMENT

The management is with all five antituberculosis drugs— (1) streptomycin 0.75–1 g intramuscularly, (2) rifamycin 450–600 mg, (3) isoniazid 300 mg, (4) pyrazinamide 1.5 g, and (5) ethambutol 800–1200 mg/day. Unfortunately, the presence of liver dysfunction complicates management. Very often it is impossible to use rifamycin and/or isoniazid as liver function deteriorates further; pyrazinamide may also worsen liver function and may have to be stopped. One is then left with second line drugs like ethionamide, clarithromycin, PAS or cycloserine. Quinolones should be added to the drug regime in patients who cannot tolerate the first line drugs.

Critical care in these patients involves efficient ventilator support, inotropic support for the circulation, maintenance of pH and arterial blood gases, and maintenance of fluid and electrolyte balance. Repeated packed cell transfusions are necessary to keep the hemoglobin at more than 9 g/dL. Nutrition is of utmost importance, and patients with GI dysfunction may need IV alimentation till oral feeds can recommence.

It is remarkable that even with significant multiple organ dysfunction, the prognosis is not as bad as is observed with Gram-negative bacterial sepsis. If patients can tolerate the first line drugs, if liver function does not progressively deteriorate, and if expert critical care is available, the mortality is around 50%. Mental obtundation, iatrogenic infection and persistent lactic acid acidosis are important features that point to a poor prognosis and a fatal outcome.

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SEVERE TYPHOID (ENTERIC) FEVER

Typhoid and paratyphoid fevers are caused by specific species of the Gram-negative bacillus, *Salmonella enterica*. Typhoid fever is caused by contamination of food or water by the *S. typhi*. This bacillus is excreted in stools and urine of acutely infected individuals and by chronic and convalescent carriers. Bad hygeine allows effluents containing infected stools and urine to contaminate food and water. Though the disease is well-nigh eliminated in the developed countries of the West, it is endemic in all poor developing countries. There are an estimated 12 million cases of enteric fever in the world each year with about 200,000 deaths.[1]

On ingestion of contaminated food or water, the typhoid bacillus is first localized in the Peyer's patches of the small intestine. It then reaches the mesenteric lymph nodes and gains entry to the bloodstream through the thoracic duct. A transient initial bacteremia occurs and the bacilli are seeded within reticuloendothelial sites where intracellular multiplication of the bacillus occurs during a 7–14 day incubation period. A second bacteremia is now observed with the bacilli again reaching the Peyer's patches in the intestine as also other reticuloendothelial sites, as in the liver, spleen, bone marrow and reticuloendothelial cells in the other organ systems. This second bacteremia is associated with fever and other systemic features that characterize the disease. The multiplication of bacilli occurs chiefly within macrophages. Inflammation within Peyer's patches leads to necrosis with formation of multiple ulcers in the ileum which are responsible for GI symptoms such as diarrhea, GI bleeds and perforation.

The reader is referred to another text for a full description of typhoid which is typically characterized at the end of the first week by continuous fever (with little and no diurnal variation), headache and malaise. Rose spots on the chest so frequently described in Western texts are only rarely observed in dark-skinned individuals. Hepatosplenomegaly is generally present.

COMPLICATIONS REQUIRING CRITICAL CARE[2]

Gastrointestinal Bleeds

The typhoid ulcers in the region of the Peyer's patches of the ileum are due to inflammation (macrophages, mononeuclear and lymphocytic infiltration) with ischemic necrosis. Ulceration of a vessel within the ulcer can produce severe GI bleeds characterized by melena or fresh blood through the rectum. It is easy to recognize this complication in the presence of fever. However, many patients today are treated within the first 4–5 days of typhoid fever (without realizing that the fever is typhoid) with antibiotics, which act against typhoid. The fever subsides but typhoid ulcers once formed run their natural course—they either heal, or bleed or perforate. When a GI bleed or perforation occurs many days after fever has disappeared, the relation of these complications to typhoid is often missed.

Typhoid GI bleeds can be severe, but rarely exsanguinating. Packed cell infusion may be necessary together with the antibiotic regime described later.

Perforation[3]

Typhoid ulcers have a greater chance of perforation compared to tuberculous ulcers or ulcers due to other pathologies. This is because ulceration due to typhoid fever is characterized by inflammation and a degree of vasculitis without any evidence of fibrosis.

Perforation is characterized by a sharp increase in pain, tenderness and guarding over the abdomen. It may be difficult to diagnose as many patients have a constant degree of abdominal discomfort with soreness on palpation of the abdomen.

Once clinically suspected and confirmed by imaging, surgery is the answer. The perforation is closed with appropriate sutures and a peritoneal toilet performed. Very often a number of other ulcers in the ileum which appear to be on the verge of perforation are also oversewn to prevent subsequent perforation. Even so, perforation may recur and in one patient three laparotomies were necessary before the patient eventually recovered.

Severe Sepsis

This is occasionally observed and can occur abruptly after the fever has lasted for 8–10 days without specific treatment. Sepsis is characterized by multiple organ dysfunction—chiefly hypotension, ARDS and severe mental obtundation with lactic acid acidosis. Recovery is generally possible if the appropriate antibiotics are given together with critical care and support to all organ systems.

Typhoid State

This is rarely seen today and was generally observed in the pre-antibiotic era in the third week of typhoid. It is still occasionally met with in patients who have not sought treatment or in those treated with indigenous drugs. The patient has high fever and displays the typhoid facies. The face is thin, flushed, with a dull apathetic expression and staring eyes. Apathy may progress to or is interspersed by muttering delirium; tremors of the hands and a tremulous often incoherent speech are observed. Osler has beautifully described the terminal stage characterized by twitching of the fingers and wrist (subsultus tendinium), plucking at bedclothes and at imaginary objects and an unrousable stupor going into coma with eyes open and staring (coma vigil). Death results from circulatory failure.

Complications Involving Other Organ Systems

The two important complications occasionally seen in severe typhoid are: (1) typhoid myocarditis and (2) typhoid cholecystitis. The latter may necessitate surgery.

Complications may however involve any organ system and a full range of complications were observed in the pre-antibiotic era. The often-repeated dictum in the Oslerian era was that if you knew typhoid, syphilis and malaria you knew your medicine. Fortunately the numerous complications of typhoid described in that era are hardly ever observed.

In children, there is a greater incidence of diarrhea, nephritis and typhoid meningitis when compared to adults.

Reports from Indonesia and Papua New Guinea have reported a subgroup of patients with severe typhoid, who present with shock (systolic BP <90 mm Hg) and poor skin, cerebral and renal perfusion with a fatality of about 50%. The criteria for what was termed severe typhoid were mental confusion and shock.[4] These are almost certainly patients with fulminant sepsis caused by *S. typhi*.

Interestingly, it was observed that in addition to chloramphenicol these patients responded to high doses of dexamethasone—3 mg/kg infused over 30 minutes followed by 8 doses of 1 mg/kg every 6 hours. The mortality in those receiving the above treatment was reported to be 10% compared to 56% in the group not receiving dexamethasone.

DIAGNOSIS

The definitive diagnosis of enteric fever is a positive culture of *S. typhi* or *S. paratyphi* organisms from the blood. Cultures are positive in 80% of cases if enough blood is taken for culture and if the patient has not received specific antibiotics. Marrow cultures yield a slightly higher incidence of positive cultures compared to blood cultures.

S. typhi can also be cultured from the urine and the stool. Stool cultures should be interpreted with caution in the areas known to have many careers.

A strongly positive Widal test in relation to the O antigen generally indicates typhoid, but the test has many pitfalls. A fourfold rise in titer of antibodies to *S. typhi* or *paratyphi* suggests enteric fever but is too delayed to help clinical diagnosis. False positive tests are seen in patients with previous infection, vaccinated individuals and in infections with cross-reacting organisms.

Other laboratory findings include a normocytic anemia and thrombocytopenia. Leucocytosis does not occur except in the presence of perforation. The WBC count is normal, but may be leucopenic. The liver enzymes are invariably slightly raised. Hyponatremia and hypokalemia may also be observed.

DIFFERENTIAL DIAGNOSIS

The commonest cause of fever extending for more than 8 days in endemic zones is enteric fever. Differential diagnosis includes malaria, dengue, leptospirosis, scrub typhus and amebic infection. Non-infective disorders, like lymphoproliferative disease, vasculitides, should also be considered.

TREATMENT

Till recently, ciprofloxacin was the first line drug against typhoid, but there is now an increasing resistance to the drug. If the positive blood culture shows resistance to nalidixic acid it implies also a significant resistance to the quinolone group of drugs.

The current drug of choice is ceftriaxone 2 g IV twice daily for 8 days. Azithromycin 500 mg twice daily orally for 5 days also acts well.

The organism seems to have now regained its sensitivity to ampicillin, chloramphenicol and cotrimoxazole.

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FULMINANT AMEBIC INFECTION

Amebiasis is caused by the protozoan *E. histolytica* and is probably the most common cause of mortality among parasitic infections after malaria and schistosomiasis. Amebiasis is responsible for 50,000–100,000 deaths annually. The disease is endemic in tropical and subtropical regions, having a high prevalence rate in India, Asia, Africa, South America and Mexico. It spreads by the orofecal route; contamination of food and water, poor hygiene, poor sanitation and overcrowding help in its dissemination. Globally, 10% of the world's population is infected with *E. histolytica* causing significant morbidity and mortality. There are two more points worth noting—

1. Host immunity is negligible in the virginal host. The host antibody response is however useful in preventing subsequent invasive episodes.
2. Amebic infection can be fulminant in the very young, in the malnourished, in those on corticosteroids and in the immunosuppressed. We have observed fulminant amebic infections in some patients with HIV disease.

PATHOPHYSIOLOGY

The pathophysiology of amebic ulcerations of the large bowel, of amebic liver abscess and the pulmonary complications observed in amebiasis are briefly given below.

Following the ingestion of cysts chiefly through consumption of contaminated vegetables, the trophozoites develop in the small gut and are carried with the intestinal contents into the cecum and the large bowel. The trophozoites are motile amebae which attach themselves anywhere along the mucosa of the large gut (particularly in the rectosigmoid and cecum). They produce an ulceration of the mucosa because of the proteolytic enzymes secreted by them. Large flask-shaped ulcers are formed which could bleed or perforate. The trophozoites at the base of these ulcers may enter the portal circulation and reach the liver. Here the proteolytic enzymes secreted by the trophozoites produce a lytic necrosis of the liver cells resulting in one or more abscesses. A hepatic abscess is most often in the posterosuperior aspect of the right lobe of the liver. Pulmonary manifestations occur as a direct extension of the hepatic abscess through the diaphragm into the pleural space, or into the lung or into both. A left lobe hepatic abscess may extend through the diaphragm into the pericardium and rarely into the left pleural space. Rarely, trophozoites may enter the systemic circulation via the rectal venous plexus so that there is a hematogenous spread of infection to the lung and, very occasionally, to other organ systems, particularly the brain. There are some who believe that hematogenous spread could also occur if the trophozoites of a liver abscess gain access to the hepatic veins or the inferior vena cava. Lymphatic spread of amebic infection from the liver through the diaphragm into the thorax remains a theoretical possibility.

In our series, more than 60% of patients with a large liver abscess had serious pulmonary manifestations. It is uncommon to find overt manifestations of amebic ulcerative colitis in patients who have pulmonary manifestations of amebiasis.

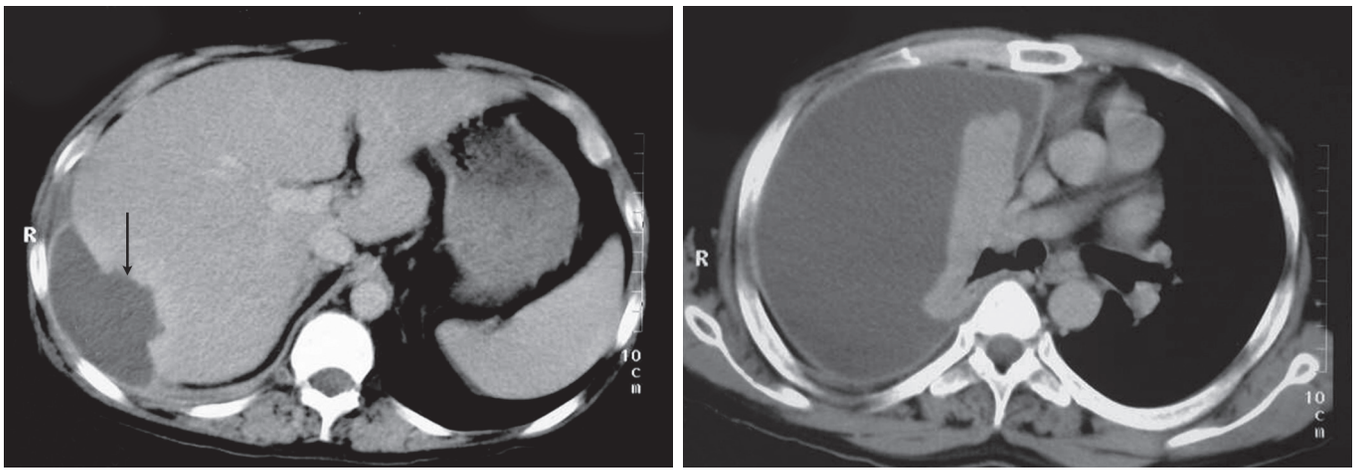
Amebic infection requiring critical care is an acute necrotizing ulcerative amebic colitis, and amebic liver abscess or abscesses which produce life-threatening complications.

ACUTE NECROTIZING ULCERATIVE AMEBIC COLITIS

Acute necrotizing ulcerative amebic colitis carries a high mortality, particularly in poor malnourished elderly patients admitted to ICUs of large teaching hospitals in the country. Death in these patients is due to perforation of the large bowel; more than one perforation may be present.

Clinical Features

Watery diarrhea and abdominal cramps with blood and mucus in the stools are the prelude to colonic perforation. The clinical manifestations of sudden severe abdominal pain, tenderness, rigidity, with an evidence of a painful inflammatory abdominal mass, or of spreading peritonitis with gas under the diaphragm are easy to recognize. However, in a number of instances, the clinical signs of perforation are atypical. This is particularly observed in poorly nourished, immunocompromised, or old debilitated patients. Such a patient looks ill; his sensorium is often clouded; he is dehydrated and complains of vague abdominal discomfort. He usually gives a history of loose watery stools for some days, but poverty, ignorance and apathy may sometimes combine to make him deny a history of significant diarrhea. Clinical examination reveals a distended abdomen with diffuse tenderness on palpation. Distension in acute amebic colitis is always to be viewed with suspicion as it is often a sign of impending perforation. When perforation occurs, distension increases and bowel sounds become feeble or absent. Watery diarrhea from a necrotic large bowel may however persist and fool the unwary into complacence. A toxic look, not unlike that observed with a toxic megacolon complicating nonspecific ulcerative colitis, is observed terminally in some patients. Fluid and electrolyte disturbances are always present. Increasing tachycardia, hypotension, shock and death ensue. A leucocytosis may not always be present. One has often wondered why the clinical features of amebic perforation of the large bowel are so atypical in some patients. The probable answer lies in the host-parasite relationship. A fulminant infection in dehydrated, malnourished, or immunocompromised patients literally swamps the body defenses and does not allow any worthwhile defense reactions to manifest themselves. The presence of a mild icterus and a palpable tender liver further strengthen the diagnosis. An associated liver abscess is easily picked up



Figs 5A and B: Ruptured liver abscess: (A) CT scan through liver demonstrates ruptured liver abscess (arrow); (B) the ruptured abscess has extended into right pleural space and caused shift of the mediastinum to the left

by an ultrasound or CT of the abdomen. A sigmoidoscopy is invaluable as amebic ulcers are always seen; amebae can be demonstrated in scrapings of these ulcers.

Management

Treatment for a perforated amebic ulcer of the large bowel or rectum is surgery for the perforation, together with specific antiamebic treatment. The prognosis in perforation is indeed poor. The friability of the large bowel adds to the surgeon's difficulties, the sutures often cutting through when the perforation is sealed. The possibility of multiple perforations must always be brought to the surgeon's attention. Remarkably enough, amebic liver abscess is uncommon in patients with necrotizing colitis. Postoperative complications are frequent and require overall critical care.

Specific Treatment

Metronidazole 500 mg IV 8 hourly is administered for 10 days. This drug is an extremely valuable amebicidal drug, and is also effective against anaerobes. Side effects include a metallic taste in the tongue, disturbances in higher functions and occasionally seizures.

Dehydroemetine 60 mg IM daily for eight injections was the drug used before metronidazole came on the scene. It is perhaps more toxic than metronidazole but was reasonably effective. Unfortunately, the drug is no longer available. Perhaps a combination of dehydroemetine and metronidazole may work better than either one or the other in fulminant amebic infections.

Tetracycline 250 mg 6 hourly is a useful adjunct in the treatment. It acts by modifying the bacterial flora necessary for the survival of *E. histolytica*. Suitable broad-spectrum antibiotics need to be given to counter the peritonitis produced by a colonic leak.

Fluid and electrolyte imbalance must be promptly rectified.

AMEBIC LIVER ABSCESS

Amebic liver abscess is an extremely common pathology in tropical countries. There are however two groups of patients with amebic liver abscess who require critical care.

(1) Those with a large undiagnosed solitary abscess, or multiple liver abscesses causing a life-threatening illness. Fever may be high and spiking, or may be low grade. The diagnosis is promptly made in a good unit, both on clinical examination and on an ultrasound of the abdomen. A tender liver, intercostal tenderness, signs of a pleural rub or pleural effusion on the right side with a raised right dome of the diaphragm, segmental or plate atelectasis in the lower lobe of the right lung are all pointers to the clinical diagnosis. A large centrally placed abscess or multiple small abscesses not approaching the diaphragm may not produce signs in the chest. A left lobe abscess may cause involvement of the left pleural space. Multiple liver abscesses or a single huge abscess can produce increasing jaundice and progressively increasing liver cell dysfunction. This is particularly seen in the malnourished, in alcoholics, and always in the cirrhotic. The patient becomes increasingly dull, apathetic and finally moribund, from a combination of sepsis and liver cell failure.[1,2]

Diagnosis[5-8]

The amebic nature of the liver abscess is proven by the indirect hemagglutinin test which is strongly positive in almost all patients with an amebic abscess. A positive test may persist even well after the abscess has completely healed. An aspirate only rarely shows vegetative form of *E. histolytica* as these forms are generally present along the walls of the abscess rather than in the anchovy sauce pus. However, *E. histolytica* can be detected from the pus of a liver abscess by the PCR technique.

Imaging with USG and CT scan help to give the exact size, number and location of the amebic abscess or abscesses (Figs 5A and B).

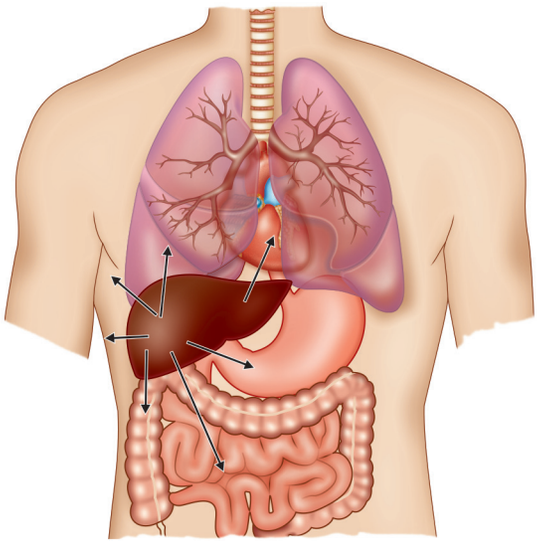


Fig. 6: Possible site of rupture of an amebic liver abscess (see text)
Source: Vakil RJ, Udwadia FE. 1982. Diagnosis and Management of Medical Emergencies. Mumbai: OUP;1982.

Box 5: Indications for aspiration of a liver abscess

- An abscess greater than 10 cm in size—aspiration allows early resolution
- A left lobe abscess greater than 7 cm; a left lobe abscess abutting on the dome of the diaphragm; presence of signs of impending rupture into the pericardium
- Lack of clinical improvement after 4–5 days of specific therapy even if abscess is less than 10 cm in diameter
- Impending rupture into the pleural space
- Seronegative liver abscess (often a pyogenic liver abscess)
- Percutaneous drainage may be necessary when—
  - The abscess is very large
  - Fills repeatedly after tapping
  - Thick pus which is not easily aspirated through a needle, as in patients with a pyogenic liver abscess

Management[9-11]

Management lies in the CT-guided aspiration of one or more large abscesses (>8 cm in diameter) and the use of specific antimicrobial treatment described earlier.

(1) Abscesses less than 8–10 cm in diameter often heal satisfactorily following the use of IV metronidazole and may not need to be aspirated.

General supportive care toward circulatory respiratory and other organ systems is necessary.

(2) Those with rupture of a liver abscess. This is a life-threatening emergency requiring critical care (Fig. 6).

Rupture may occur into the following sites—

- Into the peritoneal cavity, producing features of acute peritonitis. In some patients, the florid features observed with bacterial peritonitis may be absent, so that there is a moderate delay in diagnosis. A laparotomy is mandatory. Large drains are kept in the peritoneal cavity; the liver abscess must also be drained. If diagnosis and exploratory laparotomy are delayed, multiple organ system failure occurs and death ensues. If diagnosis is quick and treatment is prompt, recovery is possible even if multiple organ dysfunction occurs in the postoperative phase.
- Along the right paracolic gutter with tenderness in the right flank and over the right iliac fossa. A wrong diagnosis of an acute appendicitis is often made. Surgical opinion should always be sought; an exploratory laparotomy may be necessary.
- The abscess may point through the intercostal spaces to the outside, either in the anterior or mid-axillary line.
- Into the lesser sac and subphrenic space, causing a subphrenic abscess. A CT-guided drainage, drainage through the use of a pig-tail catheter or drainage tube, or open surgical drainage is necessary.
- Into the stomach, duodenum or colon; this is very rare, and surgical advice should be sought.
- Into the right pleural space causing an empyema, or into the lower lobe of the right lung resulting in a lung abscess. A left lobe liver abscess may produce the same complication in the left pleural space and/or lower lobe of the left lung. The patient may cough up anchovy sauce pus. Management consists of repeated pleural taps to keep the pleura dry. The abscess within the liver should also be drained. A right lobe liver abscess can also produce a right lower lobe consolidation, or a bronchopneumonia involving the lower lobe of the right lung. A left lobe liver abscess could produce similar pleuropulmonary consolidations involving the left lung.
- Into the pericardium—this is one of the most dreaded of medical emergencies, and is rapidly fatal. Rupture into the pericardium invariably occurs from a left lobe liver abscess close to the diaphragm. Unexplained well marked tachycardia and/or a pericardial rub are often warning signs of the impending rupture. Pain over the left shoulder which worsens on deep breathing is another warning sign. Intrapericardial rupture leads to acute dyspnea, and quickly evolving cardiovascular collapse. Heroic measures can however save the patient. The pus in the pericardial space must be promptly aspirated percutaneously and the liver abscess must also be quickly drained. The help of a thoracic surgeon must be sought so that open drainage of the pericardium can be performed, if percutaneous aspiration is inadequate.

In addition to surgical attention and adequate drainage outlined above specific antiamebic treatment should also be given. It is to be noted that a huge liver abscess (for example, one occupying the greater part of the right lobe or one which fills repeatedly after tapping) may require drainage through a large drainage tube left in situ. The danger of introducing secondary infection is ever present in this situation. Indications for aspiration of a liver abscess are given in Box 5.

Prognosis

Though most patients with complicated amebic liver abscess recover if diagnosed quickly and adequately treated, deaths do occur. Bad prognostic features are deepening jaundice with bilirubin levels greater than 7 mg/dL, poor response to specific therapy, multiple abscesses or a single very large abscess occupying the greater part of the lobe of the liver, mental obtundation and encephalopathy and persistent hypoalbuminemia. There are reports of vegetative forms of *E. histolytica* which have developed a degree of resistance to metronidazole. Death is due to rupture into the peritoneal cavity (with delayed diagnosis), multiorgan failure, and rarely due to metastatic spread of amebic infection, particularly from amebic abscesses in the brain.

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DENGUE HEMORRHAGIC FEVER

INTRODUCTION

Dengue hemorrhagic fever is a mosquito-borne (*Aedes aegypti* is the carrier), flavivirus infection which afflicts 500,000 patients per year throughout the tropical regions of the world.[1,2] Depending on epidemic activity, dengue and dengue hemorrhagic fever are observed with varying frequency in all parts of India. The average mortality is 5%; the fulminant forms carry a much higher mortality. The disease can be caused by any one of the four distinct dengue viruses—DEN-1, DEN-2, DEN-3, DEN-4. Infection caused by one virus does not necessarily confer immunity to any one of the other viruses.

PATHOGENESIS[3,4]

The pathogenesis underlying the features of dengue hemorrhagic fever is based on the presence of subneutralizing levels of dengue antibodies in the blood. This enhances the infectivity of a fresh dengue viral infection by increasing the binding and uptake of virus-antibody complexes through the Fc receptors on monocytes in the blood and on tissue macrophages. The immune response also involves cellular activation, with cytokine release and activation of complement. It is this primed immune response which is response for widespread capillary leakage, coagulopathy with extensive hemorrhagic manifestations and acute circulatory failure—the hallmarks of the illness.

CLINICAL FEATURES[3-5]

The clinical features are characterized by the sudden onset of fever, bodyache and headache. It is impossible to distinguish this presentation from other tropical infections at this stage. The suspicion of a viral infection is generally entertained by the presence of well-marked leucopenia (the WBC count may fall to less than 2,000/mm^3) and increasing thrombocytopenia. These early hematological features in a febrile patient should prompt the diagnosis of a possible dengue viral infection, more so in the presence of an outbreak of dengue in a particular area or district.

After 2–7 days, there is a defervescence in the fever and at this crucial time the classic features of this infection are observed with varying degree and intensity. These are: (1) hemorrhagic manifestations due to thrombocytopenia and coagulopathy; (2) widespread capillary leak and (3) acute circulatory failure—the dengue shock syndrome.

Hemorrhagic features are present in varying degree, the most common being purpuric lesions and ecchymosis. However, bleeding from thrombocytopenia, coagulopathy and capillary damage often takes the form of severe epistaxis, hematemesis and hematuria. We have observed bleeding into the pleural space, peritoneal cavity and into any organ system, including the brain. Fulminant dengue hemorrhagic fever is associated with disseminated intravascular coagulopathy with widespread bleeding tendency.

The capillary leak is manifested by edema of the feet and of the subcutaneous tissue, crackles over the lung bases which may at times progress to non-cardiogenic pulmonary edema, leading to acute lung injury and ARDS. Pleural effusions occur in severe cases and are a manifestation of the capillary leak syndrome. They are often an accompaniment of dengue shock. The pleural fluid does not contain inflammatory cells, is rich in albumin, the albumin content being over 60% of that in blood. Objective evidence of a capillary leak is provided by the presence of hemoconcentration (the hematocrit being elevated by 10–30%).

Acute circulatory failure is characterized by the clinical features of shock. Tachycardia, tachypnea, hypotension, oliguria, mental obtundation, lactic acid acidosis are all observed. Elevation of liver enzymes is invariably present; in fact liver enzymes are often raised well before the onset of hemorrhagic manifestations. Increasing serum bilirubin with progressive liver cell dysfunction may be observed. Evidence of multiple organ dysfunction is frequent and progressive in fulminant fatal cases.

The duration of shock lasts for 2–4 days, culminating in recovery or death. Death can also occur from a severe bleed into an organ system (e.g. brain) or from multiple organ failure. Myocardial involvement is evinced by poor systolic function on an ECHO study; stupor or coma due to encephalitis invariably points to a fatal end.

DIAGNOSIS

The diagnosis depends on the demonstration of IgM antibodies (by the ELISA technique) to the dengue virus. Unfortunately, not all patients develop IgM antibodies within the first week of the infection. In some patients a rise in IgM is observed after as long as 10 days. The Dengue antigen is positive within the first 3–4 days of the infection.

Differential diagnosis of acute hemorrhagic fevers in the tropics may pose problems. Important infections other than dengue hemorrhagic fever that merit consideration are meningococal sepsis and meningitis, fulminant Gram-negative infections causing a coagulopathy, fulminant falciparum infection, acute leptospiral infection, severe rickettsial infection, fulminant viral hepatitis, bacterial endocarditis and hemorrghagic exanthemas, as in hemorrhagic chicken pox and measles. Consideration of the clinical background, examination of peripheral blood smears, blood cultures, serological tests and other relevant laboratory investigations generally help in diagnosis.

Fortunately, hemorrhagic fevers caused by the Ebola and Hanta viruses are restricted to well-defined areas of

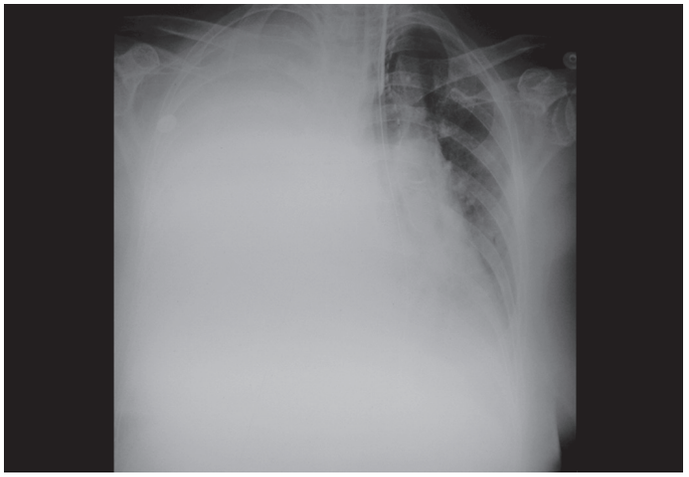

Fig. 7: Dengue—Complete opacification of the right lung likely as a result of large pleural fluid collection in a case of dengue

Africa. These highly infectious viral diseases cause fever with extensive hemorrhages, cellular death, multiple organ failure and have a mortality close to 80%.

Thrombotic thrombocytopenic purpura though rare is often mistaken for a fulminant infection causing widespread purpura (Fig. 7).

MANAGEMENT

Dengue hemorrhagic fever requires critical care; treatment is mainly supportive. No antimicrobial drug acts on the dengue virus. Hemorrhagic manifestations and coagulopathy are countered by replacement of deficient clotting factors and by platelet infusions. Anemia is corrected by infusion of packed cells. Hemorrhage into the pleural space or peritoneal cavity may require drainage.

Signs of impending shock should be detected early and treated by prompt infusion of colloids, plasma and, if necessary, by inotropic and vasopressor support. It is important to remember that shock can occur with dramatic and frightening suddenness. Oxygenation should be well maintained and the delivery of oxygen to the tissues should be adequate. It is important to insert a central venous catheter early in the natural history of the disease, as puncture sites can bleed profusely. Volume replacement is guided by clinical examination and by measuring central venous pressure. Over-infusion of fluids can precipitate or worsen ARDS. The difficulty arises when one is confronted with the capillary leak syndrome as manifested by edema and crackles over the lungs and progressive hypotension. An excessive fluid load with the purpose of reducing the hematocrit concentration to 40–45% can precipitate ARDS. One may need to temporize by using a judicious combination of IV fluids + inotropic and vasopressor support. Once shock has been effectively countered, a small titrated dose of IV frusemide reduces pulmonary congestion. If ARDS does occur in spite of all efforts, it is managed on conventional lines with intubation and appropriate ventilator support. Ventilation support is also necessary in patients who are in shock and acute circulatory failure. A combination of severe ARDS + severe hypotensive shock is of grim prognosis.

Metabolic acidosis is frequent and should be corrected. All organ systems must be given adequate support.

Secondary bacterial nosocomial infection is observed in some patients, requiring suitable antibiotic treatment. A combination of severe dengue with a superadded acute bacterial (generally Gram-negative) infection carries a very grave prognosis. Death occurs due to rapidly progressive multiorgan failure.

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SEVERE LEPTOSPIROSIS

INTRODUCTION

Leptospirosis is a worldwide zoonosis afflicting many mammals; rodents form the most important animal reservoir. The disease is common in the tropics and is frequently observed in India, Southeast Asia, Africa, and South America. It is caused by a spirochete, the pathogenic species being the *Leptospira interrogans*. There are several serotypes of this genus; some of these preferentially infect select mammalian hosts. Thus, the serotype *L. icterohemorrhagica* is associated with the rat, *L. canicola* with dogs and *L. pomona* with swine and cattle. Leptospira are excreted through the urine of the infected mammalian hosts. Transmission of infection from animal to man generally occurs through contaminated water or moist soil. Leptospira enter through abrasions in the skin (generally on the feet and legs), or rarely through the mucosa of the mouth, pharynx or esophagus. The disease is therefore common in the monsoon, particularly at the time of floods, in areas where there is a large population of rats.

In most cases, human infection is asymptomatic or mild and cures itself. However, 5–15% of cases are severe or fatal.[1]

PATHOGENESIS[2]

The organisms, after gaining entry, generally through abraded skin, enter the bloodstream and are distributed to all organs of the body. The fulminant forms always severely affect liver function and often produce varying degrees of renal dysfunction. Leptospira can persist for months in the kidneys and ocular tissue.

The exact pathogenesis is unexplained as there are minor histopathological changes in the liver or kidney or other organ systems in the presence of severe functional derangement.

CLINICAL FEATURES[1,3-7]

The severe and fulminant forms of the disease are observed in icteric leptospirosis (Weils disease). The illness is ushered by fever, headache, severe muscle pains and marked conjunctival injection. Jaundice with impaired liver cell function appears by the fifth to seventh day and may persist for a month. However, death is very rarely related to liver cell failure.

All or many organ systems are affected. The most important organ involved is the kidney. Albuminuria, RBCs are invariably present. Oliguria with acute renal failure occurs in severe cases.

The lungs frequently show hemorrhagic bronchopneumonia. We have seen a few patients presenting with acute intra-alveolar hemorrhage that can cause death from overwhelming hypoxia, unless the patient is promptly intubated and ventilated with a high FiO_2. Intra-alveolar hemorrhage may be the presenting feature of severe disease.[3,4,7] ARDS is an important feature of severe leptospiral disease.

Meningitis (the CSF showing pleocytosis with raised protein) is frequently observed. It is likely that meningeal involvement may be related to an immunological mechanism than to actual invasion of the leptospira in the meninges. Organisms may be found in the CSF without meningeal or CNS symptoms. An obtunded mental state is either due to aseptic meningoencephalitis or due to uremic encephalopathy.

Fulminant leptospirosis is characterized by a hemorrhagic diathesis. Petechiae, epistaxis, subconjunctival hemorrhage, hemoptysis are common manifestations. Death can occur from subarachnoid hemorrhage or from exsanguinating GI bleeds. A coagulopathy with raised prothrombin time and thrombocytopenia is frequent. Bleeding is related both to the coagulopathy and to capillary damage. The overall clinical picture in its fully evolved form often resembles Gram-negative bacterial sepsis.

There is marked leucocytosis in the peripheral blood; WBC counts as high as 30,000/mm^3 or more may be observed.

DIAGNOSIS[8-11]

The diagnosis should be suspected on clinical grounds in endemic areas. The triad of fever, conjunctival injection with subconjunctival hemorrhage and jaundice should arouse immediate suspicion. A further association of abnormal urinary findings with varying degrees of renal insufficiency renders the diagnosis even more likely. Muscle pains associated with muscle tenderness are observed in close to 80% of patients. This is invariably associated with very high creatine phosphokinase (CPK) levels in blood. Patients presenting with fever and intra-alveolar hemorrhage invariably in our experience have very high CPK levels—a combination almost diagnostic of severe leptospiral disease. Leucocytosis is almost always present, but does not help in diagnosis.

The IgM for leptospiral infection (done by the ELISA technique) is generally positive by the fifth to seventh day.[8] Immunofluorescent assays are also being used for diagnosis. Serological tests for diagnosis are also available but these have poor sensitivity.[10] The PCR test for leptospirosis can help in diagnosis; we have no experience of its use. It is only done in special reference laboratories.[9,11]

The main differential diagnosis is sepsis caused by other organisms, fulminant viral hepatitis and fulminant *P. falciparum* infection. The latter does not generally cause deep jaundice. When meningitis is a presenting feature the disease has to be distinguished from other forms of aseptic meningitis and from tuberculous meningitis. Patients presenting with acute intra-alveolar hemorrhage need to be distinguished from acute Wegner's granulomatosis, systemic lupus erythematosus and other connective tissue disorders (Fig. 8).

Fig. 8: Leptospirosis—Chest X-ray shows multiple fluffy opacities in both lung fields as a result of fulminant leptospiral infection

TREATMENT[3,12]

Treatment in severe cases should be started on clinical suspicion. It should never await a laboratory diagnosis. Antibiotics should be used early in the course of the illness—by the 4th day. Penicillin G is the drug of choice; 2 million units 6 hourly are given IV for 8–10 days. Tetracycline (25–40 mg/kg per day) given every 6 hours and doxycycline 100 mg twice daily for 8–10 days are also effective. It should however be noted that a Cochrane systemic review failed to find sufficient evidence to provide clear guidelines for the use of antibiotics.[12]

Intra-alveolar hemorrhage requires intubation and ventilator support. There is a dramatic improvement in the clinical state, chest X-ray and arterial oxygenation following pulsed therapy with 1 g methylprednisolone IV daily for 3 days, followed by oral prednisolone (40 mg/day), tapered and stopped after 10 days. This dramatic improvement occurs within a few hours of the administration of the drug. Acute renal failure may warrant dialysis till recovery ensues.

Critical care is vital, with support to all organ systems. Fresh frozen plasma and platelet infusions are necessary to treat coagulopathy. Patients with severe leptospirosis need correction of hypovolemia, inotropes and vasopressors to counter hypotension. Fluid and electrolyte balance should be well maintained.

Acute respiratory distress syndrome requires intubation and appropriate ventilator support.

Patients with acute renal failure may require hemodialysis till such time as the kidney recovers.

If the patient recovers, kidney function and liver function return to normal. However, anterior uveitus may occur days or weeks after recovery or may persist if present during the course of the acute illness.

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SCRUB TYPHUS

INTRODUCTION

Scrub typhus is a zoonotic disease of rural Asia caused by a Gram-negative intracellular bacterium orientia (formerly Rickettsia). This organism is transferred from rats to humans by the bite of a larval mite (chiggers) which has fed on an infected rat. It is believed that more than a billion people are at risk and a million cases are transmitted annually, making it the commonest Rickettesial disease.[1] Disease transmission occurs when infected mites burrow into the skin, feed on tissue fluid and inoculate the infective bacterium. The disease is uncommon in large metropolitan cities, but even so does occur, and is frequently misdiagnosed. It is endemic in all rural areas of India and is particularly observed in the North, Northeast and Eastern part of the country.

CLINICAL FEATURES[1]

More often than not the disease is mild, short lasting and easily missed. In its typical form it is characterized by fever, myalgia, conjunctival suffusion, generalized lymphadenopathy and the presence of an eschar (which is really an ulcer covered by a thick crust) at the site of the tick bite. The eschar is however present in not more than 50% of primary infections. There are other features which should suggest the diagnosis even in the absence of a typical eschar. These are a truncal macular or maculopapular rash which spreads peripherally, hearing loss concurrent with fever, persistent cough with bilateral reticular infiltrates at both bases on radiography of the chest.

Though most cases are mild, severe cases meriting critical care do occur. These patients develop or present with dyspnea, a progressive increase in the respiratory rate, tachycardia and a fall in O_2 saturation. They may develop a full blown ARDS.

High temperature, apathy, confusion may be observed and rarely these may progress to stupor, seizures and deep coma.

DIAGNOSIS[2]

The presence of an eschar is diagnostic but as mentioned earlier it is present only in 50% of cases. Also, an eschar even if present may be missed or misdiagnosed. It should be searched for carefully, particularly in moist areas of the skin, as in the axilla or the groin. Laboratory features which suggest the diagnosis, include a mild leucocytosis, atypical lymphocytes in the peripheral smear and a mild to moderate elevation of liver enzymes.

The differential diagnosis is from dengue, other viral infections and leptospirosis. The critically ill patients with scrub typhus may mimic severe typhoid. The latter does not cause conjunctival suffusion, a macular rash or generalized lymphadenopathy so often observed in scrub typhus. It is not uncommon for a patient to suffer a dual infection—in particular a dual infection of leptospirosis and scrub typhus.

The Weil-Felix test using the OXK antigen is widely used but insensitive. The indirect immunofluorescent assay and the immunoperoxidase tests are confirmatory tests but are performed only in a few reference laboratories. A rapid dot blot immunoassay not requiring a microscope has also been developed. Unfortunately there is no easily performed available test that can be used in rural areas where scrub typhus is endemic.

TREATMENT[3,4]

In pre-antibiotic days, the fatality rate was as high as 30%. Present antibiotic therapy offers a quick cure, lowers the risk of ARDS and has sharply reduced mortality. More often than not treatment is based on a clinical assumption of the diagnosis. Tetracycline 500 mg four times a day or doxycycline 100 mg twice daily for 7 days is recommended. In critically ill patients parenteral doxycycline or parenteral tetracycline or IV chloramphenicol (50–75 mg/kg per day) is administered. Critically ill patients may require ventilator support as also support to other organ systems.

Azithromycin is the drug of choice in pregnant women with scrub typhus or in children who contact the disease, as both tetracycline and doxycycline are contraindicated in the above situation. Azithromycin has also proved successful in patients with drug-resistant scrub typhus.

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MELIOIDOSIS

INTRODUCTION

Melioidosis is an infection caused by the saprophytic bacterium *Burkholderia (B.) pseudomallei*. It is endemic in South and Southeast Asia, the incidence being particularly high in Northeast Thailand. The country with the highest number of recorded cases is Thailand where the average incidence is 4.4 per 100,000 people. The disease is also endemic in South China, Central and South America and parts of Africa. Human infection probably occurs through contaminated scratches and abrasions or occasionally following aspiration of contaminated fresh water. Agricultural workers and rice farmers in close contact with soil and water are at greater risk. It has been reported in India, particularly from Tamil Nadu and Karnataka. Cases have also been reported from Orissa, West Bengal, Assam, Andhra Pradesh and Maharashtra.[1-4]

CLINICAL FEATURES

Melioidosis can present acutely, subacutely or present in a chronic form. It is the acute form of the disease which merits critical care and which is described briefly below. The acute form of the disease is generally observed within 2 weeks of exposure. There are three modes of presentation—

1. The first is characterized by high fever and rapidly evolving features of overwhelming sepsis. ARDS, septic shock, multiorgan failure are observed in fatal cases. The clinical picture is indistinguishable from fulminant sepsis due to other causes.
2. The second mode of presentation is again with high fever, features of increasing sepsis and the presence of suppurative disease in one or more organ systems. The lung is perhaps the most frequently involved organ, a suppurative pneumonia involving one or more lobes being observed. If undiagnosed the condition progresses to increasingly severe sepsis with multiorgan failure.
3. The third mode of presentation is that of an acute pneumonia involving one or more lobes with the frequent occurrence of suppuration and cavitation. The lung may be the only organ involved. However, in a number of patients presenting with acute pneumonia, a careful search may reveal evidence of silent abscesses in the other organs—notably the liver and spleen.

DIAGNOSIS

A clinical suspicion of melioidosis can be confirmed by a blood culture positive for *B. pseudomallei*. When the lung is involved either in isolation or as part of other organ system involvement, sputum cultures are generally positive for the organism. It is important to inform the microbiologist if melioidosis is suspected, as identification of the organism in sputum samples which have polymicrobial flora is difficult and often missed.

At times, isolation of the organism is easier from the discharge of a metastatic cutaneous lesion or from the aspirate of a metastatic liver abscess.

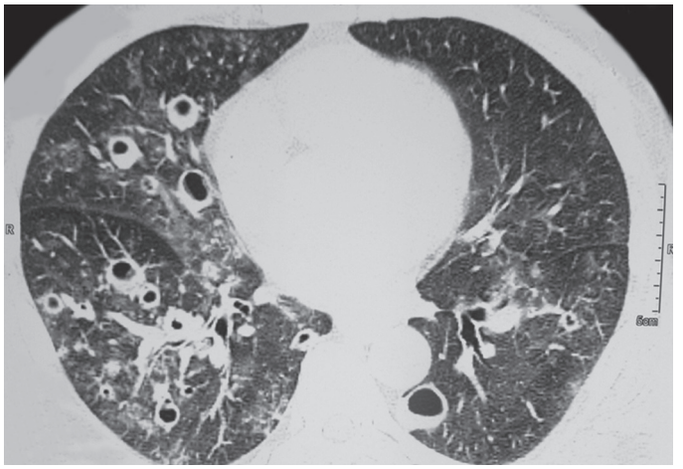

Fig. 9: Melioidosis. CT scan of the chest reveals multiple thick-walled cavitating lesions with air-fluid levels

IMAGING

Pneumonia is evident on an X-ray of the chest. A CT scan may reveal evidence of breakdown as also evidence of involvement of more than one lobe. Multiple small abscesses in different parts of the lung are missed on a radiographic examination and are visualized on a CT scan of the chest. Pleural effusions and empyema may complicate pulmonary involvement.

Imaging is helpful in revealing abscesses in other organ system—CT scan, magnetic resonance imaging (MRI) and in some instances positron emission tomography (PET) scans may be necessary to demonstrate other organ involvement (Fig. 9).

SEROLOGY

Indirect hemagglutination tests and complement fixation tests are believed to have a high diagnostic sensitivity, though we have no experience with these tests. People living in highly endemic areas, such as Thailand, have a high incidence of seropositivity for the disease. Therefore, in these areas the diagnostic titer needs to be high, preferably 1 in 640 or more to avoid false positive readings.

TREATMENT

The acute form of the disease or patients with multi-system involvement are best treated with ceftazidime in maximum

doses of 2 g IV 8-hourly together with one other antibiotic. This could be doxycycline (4 mg kg/day) or cotrimoxazole in maximal doses. The antibiotic course should be for 2–4 weeks. Following this, oral antibiotic maintenance thereby is advised for 6 months to a year. Antibiotic for maintenance therapy could either be doxycycline 4 mg/kg per day or cotrimoxazole (trimethoprin 10 mg/kg per day, sulfamethoxazole 50 mg/kg per day) or amoxycillin clavunate in high doses.

Prolonged courses are necessary because the disease is slow to respond and frequently relapses. Extrapulmonary abscesses may require surgical drainage.

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CHAPTER 46

Antibiotic Therapy in the Intensive Care Unit

GENERAL CONSIDERATIONS

Patients are often admitted to the intensive care unit (ICU) with fulminant infections. Infection is also an important complication of patients admitted to the ICU for other unrelated life-threatening problems. In either case, treatment of infection needs to be prompt, comprehensive, but above all judicious.[1]

Till three decades ago, it was believed that the array of antibiotics available at that time would take care of infections in general and of infections in the ICU in particular. This expectedly has proved to be a mirage. There is an ecological balance between microorganisms and man in a particular environment. An attempt to eradicate one group of microorganisms by the injudicious use of antibiotics breeds resistant strains in increasing numbers and is often associated with an increasing number of different unrelated infections.

In fact, today we are faced with a world-wide epidemic of antibiotic resistance, and it appears that this epidemic is likely to spread and increase in its severity even more. There are two further disturbing facts. First, among the microorganisms showing increasing resistance to antibiotics are virulent Gram-negative pathogens, which can cause life-threatening infections. Second, we have exhausted our therapeutic antibiotic armamentarium against these Gram-negative organisms, and there do not appear to be any potent new drugs in the pipeline to counter these infections. We truly live in an era characterized by what the Infectious Diseases Society of America has termed—"Bad Bugs, No Drugs"![2] And how did we come to this sorry pass? It is due to our injudicious use of antibiotics that were previously effective; an antibiotic pressure (if one may term it so) on microorganisms that made them change and become resistant to their use. Darwin's hypothesis of survival of the fittest, which applies to the evolutionary process that led to *Homo sapiens,* also appears to apply to microorganisms. In order to survive the immense antibiotic pressure imposed by man, they had to change (alter their genetic structure) if they had to survive. And change they did, very effectively so, both to our dismay and danger.

Therefore, if we must save this situation or at least not let it get worse, every ICU and hospital should frame an antibiotic policy. Good antibiotic stewardship should aim at optimal clinical outcomes yet preserving the efficacy of antibiotics in use today. The importance of education to influence doctors to change their prescribing behavior with the above objective in mind is unquestioned.[3] Antibiotic policy and stewardship is perhaps most crucial in the ICU. An unwise or injudicious policy in the ICU characterized by overuse of potent antibiotics when this is not indicated, or the unnecessary use of a combination of antibiotics may eradicate infections in patients at that point in time but at the cost of breeding resistant microorganisms. This may have repercussions for patients admitted weeks or months later. This is because resistant organisms become part of the ICU ecology and can be transmitted to other patients admitted several weeks or months later, with devastating results.

The following section very briefly discusses principles of antibiotic therapy, which aim at both effectiveness and prevention of antibiotic resistance as far as possible.

PRINCIPLES GOVERNING ANTIBIOTIC POLICY IN CRITICALLY ILL PATIENTS[4]

- Antibiotics should be used in the presence of clinical and/or bacteriological suspicion of infection. It is important

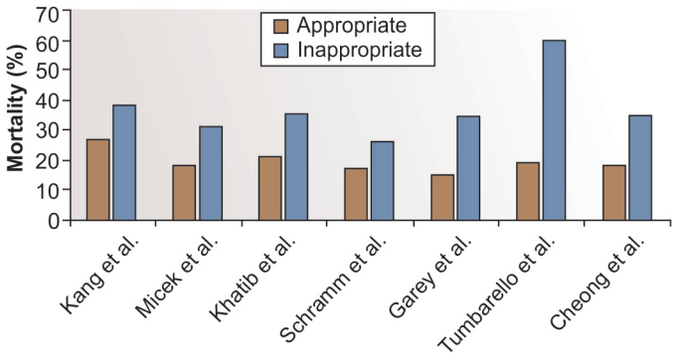

Fig. 1: The figure illustrates the increase in mortality when antibiotic therapy is inappropriate and delayed
Source: Morrell MR, Micek ST, Kollef MH. The management of severe sepsis and septic shock. Infect Dis Clin North Am. 2009;23(3):485-501.

to remember that the systemic inflammatory response (SIRS) which characterizes infection can also be caused by non-infectious causes. The use of antibiotics when the SIRS is due to a non-infectious cause does not help the patient and may even cause harm by exposing the patient to adverse effects of the antibiotic used and encouraging the growth of resistant microorganisms.

- Samples for appropriate staining and culture should be obtained from blood, body secretions and infected tissues before starting an antibiotic.
- The antibiotics chosen should be as per therapeutic protocols established for each individual ICU. Criteria for selection may vary with different ICUs, but once a selection is made, it should be followed and reviewed periodically. Criteria for selection of antibiotics in our ICU are discussed later.
- In severe life-threatening infections empiric antibiotics therapy should be started promptly after the above cultures have been taken without awaiting results. The antibiotics used should cover all likely microorganisms that could be implicated, depending upon the clinical scenario and the antibiogram of a particular ICU. The sooner treatment is started, the better—preferably within the first hour of admission. *Delay in treatment has clearly been shown to result in adverse outcomes.*[1]
- The dose of the antibiotic used should be optimized. Antibiotics, which act via time-dependent killing, are given at more frequent intervals. Antibiotics, which act through concentration-dependent killing, do so when the peak concentration is several times more than the minimum inhibitory concentration (MIC). Single dose therapy may be more advantageous.
- The choice of an antibiotic should depend not just on its efficacy against a particular organism, but its ability to reach and be concentrated at the site of infection.
- Combination therapy is used in the treatment of life-threatening infections. The reasons for combination therapy are—
  - Possible synergy against virulent particularly Gram-negative infection. Combination therapy is generally recommended in the treatment of multidrug-resistant *Pseudomonas aeruginosa*, *Acinetobacter*, *Klebsiella pneumoniae*.
  - Prevention of resistance. This again is with reference to severe Gram-negative infections—in particular *P. aeruginosa*, *Acinetobacter*. There is conflicting evidence if resistance can be prevented by using combination therapy. The general consensus is to use combination therapy when dealing with infections caused by *P. aeruginosa* or by *Acinetobacter*.[5]
  - Providing broader antibacterial coverage in life-threatening infections caused by multi-drug resistant microorganisms. This is perhaps the most important use of combination antimicrobial therapy. Empiric therapy against life-threatening infections should always be optimal and include two or even more agents in the hope that all possible organisms that could cause a particular infection are covered.
- Once the organism causing an acute infection has been identified through culture, antibiotic cover should be focused on eradicating that particular organism. In most instances, a single antibiotic of proven efficacy (as observed from the antibiogram of a particular ICU) will suffice.
- In critically ill patients, infection may be polymicrobial, e.g. in severe abdominal sepsis. All responsible organisms may be difficult to identify. Antibiotic coverage should cover against all likely aerobic and anaerobic causative organisms.
- It is important not to unnecessarily prolong antibiotic therapy. This however cannot be quantified. Though in many instances antibiotics can be stopped in 8–10 days; in other instances, they may need to be given for a much longer time.
- Clinical improvement should prompt de-escalation of antibiotic therapy.
- It is important to measure the efficacy of antimicrobial treatment. The first evaluation should be at 72 hours following empirical treatment. Worsening of the initial clinical manifestation, or evidence of new features of infection suggest that the empiric choice of the antibiotic/antibiotics is not appropriate. This should prompt fresh cultures of blood, infected secretions, or infected tissue and the use of rescue regimens with a broader spectrum of activity, so as to cover potentially multi-resistant organisms. If the early empiric therapy is deemed correct as per susceptibility testing, and the clinical course is still unfavorable, it is important to check whether the dose administered is correct, whether the antibiotic is administered at proper intervals so as to guarantee an adequate pharmacokinetic/pharmacodynamic (pK/pD) relationship,[6,7] and whether the antibiotic/antibiotics administered have good penetration into the infected tissue.
- One should be alert to the presence of adverse effects and emergence of resistant bacterial flora. Each class of antibiotics is associated with specific adverse effects.

Many adverse effects are however common to different classes of antibiotics. Also, the use of other drugs (with potential adverse effects) in critically ill individuals further complicates the problem as it may be difficult to attribute an adverse effect to one particular antibiotic.

It should be remembered that patients suffering from burns, heart failure or those who have had major surgery, frequently have an increase in body mass distribution, affecting plasma and tissue drug concentration. Drug elimination is also affected by renal insufficiency, hypotension and hemodynamic instability. All these factors influence the pharmacokinetic profile of antibiotics and may account for the large individual differences in antibiotic levels when the same dose is given to different individuals. It is therefore advisable to monitor antibiotic blood levels (whenever possible), particularly when the difference between optimal therapeutic and toxic level is small, as in the case for example with aminoglycosides and vancomycin. The introduction of pharmacokinetic model programs designed to monitor plasma drug concentrations allows adjustments in dosage to maximize clinical efficacy and yet reduces toxicity or adverse effects.[8]

The longer antimicrobials are used in a patient (particularly when more than one antibiotic is in use), the greater the chance for the development of multidrug resistant pathogens which may be the cause of treatment failure in an individual patient.

Surveillance studies with reference to culture of samples from infected foci and mucous membranes (nasopharynx, trachea and stools) are important to detect the emergence of multi-resistant bacterial pathogens.

ANTIBIOTIC RESISTANT GRAM-NEGATIVE ORGANISMS IN THE ICU[9]

It is important for the intensivist to be aware of the reasons for and the nature of increasing antibiotic resistance observed in the ICUs, if he or she is to make an informed calculated choice in the use of antibiotics—either for community acquired or nosocomial infection in the unit.

The evolution and spread of Gram-negative organisms producing extended spectrum β-lactamase (ESBL) has been responsible for an increasing number of antibiotic resistant Gram-negative infections. The extended spectrum β-lactamases are β-lactamases that confer bacterial resistance to the penicillins, first, second, third generation cephalosporins and aztreonam, by inducing hydrolysis of these antibiotics. The ESBLs are however not resistant to cephamycins or carbapenems and are inhibited by β-lactamase inhibitors such as clavulanic acid or tazobactam.

Extended spectrum β-lactamases represent an impressive example of the ability of Gram-negative organisms to develop new antibiotic resistance mechanisms, in the face of the introduction of new antimicrobial agents. Typically, ESBLs are derived from genes of *TEM-1, TEM-2* and *SHV-1* by mutations that alter the aminoacid configuration around the active site of these β-lactamases. A large and increasing number of ESBLs not of *TEM* or *SHV* lineage have also been described. Obviously, the increasing presence of ESBLs chiefly in ICUs and hospitals as also in the community is of great clinical significance, as antibiotic options in the treatment of ESBL producing organisms are markedly limited. The ESBLs are frequently plasmid encoded and plasmids responsible for ESBL production very often carry genes encoding resistance to other drug classes, e.g. aminoglycosides. Equally important is the fact that ESBL producing organisms are also often resistant to the quinolones—not just to ciprofloxacin but to other quinolones as well.

The ESBLs appeared on the medical scene in 1983. Reports came chiefly from Europe—Germany, France and the United Kingdom. By now, they have spread and have been reported from all over the world. It has been shown through genotyping that ESBLs can spread from one ICU to the hospital wards, from one hospital to another in the same city, from one city hospital to other hospitals in the country and also from country to country.

In India, there has been a tremendous increase in infections caused by ESBLs in ICUs all over the country. About 40–80% of organisms isolated in the ICUs are now ESBLs, pointing to the ever-increasing number of potentially antibiotic resistant infections.[10]

What is frightening is that ESBL producing gram negative organisms, as also Ps. aeruginosa, Kl. pneumoniae, Acinetobacter previously sensitive to the carbapenems are now showing increasing resistance to the latter because of their over-use. Also, the selection of intrinsically carbapenam-resistant organisms, such as Stenotrophomonas maltophilia and Enterococcus faecalis, is on the rise.

Risk Factors for Colonization and Infection with ESBL Producers[9]

Risk factors include—

- Seriously ill patients with prolonged hospital stay in whom invasive medical devices are present. Parenteral nutrition, recent surgery, hemodialysis, poor nutritional state, decubitus ulcers are other important risk factors.[9]
- Heavy antibiotic use is a major risk factor. Several studies have shown a relation between use of third generation cephalosporins in particular ceftazidime and the acquisition of ESBL producing organisms. Use of a variety of antibiotic classes have been found to be associated with subsequent infections due to ESBL producing organisms. These include aminoglycosides, quinolones, metronidazole and trimethoprim sulfamethoxazole. Conversely, prior use of penicillins, β-lactam-β-lactamase inhibitor combinations and carbapenems are not frequently associated with ESBL infection.

One is therefore left with the option of either using a β-lactam-β-lactamase inhibitor or the use of carbapenems in the treatment of ESBL infections.[9] It should be noted that

β-lactam-β-lactamase inhibitor combinations are effective against ESBLs producing a single β-lactamase. However, many Gram-negative ESBL organisms produce multiple ESBLs; this reduces effectiveness of β-lactam-β-lactamase inhibitor combinations.[9] Also the MIC against β-lactam-β-lactamase inhibitor at times depends on the inoculum, the MIC increasing markedly if the inoculum is increased.[9]

To worsen the nightmare of antibiotic resistant organisms, there has recently been slowly, but definitely increasing resistance of Gram-negative organisms to the carbapenems. Strains of *K. pneumoniae, P. aeruginosa*, *Acinetobacter* are now increasingly resistant to this class of antibiotics This can happen under the following circumstances[11-13]—

- When there is combinations of ESBL production and porin loss.
- When the organism produces carbapenemases—these are metalloenzymes, which render the carbapenems ineffective.
- When there is a change in the affinity of penicillin binding proteins to the carbapenems.

We are now left with colistin and polymyxin as our only weapons against Gram-negative organisms resistant to the other classes of antibiotics. There have been reports from an ICU in Delhi[14] of emerging colistin resistance as well. When colistin resistance indeed transpires on a large scale, the nightmare will become a grim reality.

Fortunately, the problem of methicillin-resistant *Staphylococcus aureus* (MRSA) infections is comparatively uncommon when compared to the West (except perhaps in a few units). Also, there are newer drugs available, which can as yet counter these infections. Intermediate resistance of MRSA to vancomycin and even complete resistance to vancomycin have now been observed. Vancomycin resistant enterococci, which however are responsive to the use of linezolid, should also be kept in mind.

REASONS FOR INCREASING MULTI-DRUG RESISTANT GRAM-NEGATIVE INFECTIONS

Why is there a continuing increase in multi-drug resistant Gram-negative infections in the ICU?

The basic reasons as already stated are overuse of antibiotics, inappropriate use of antibiotics, poor or absent antibiotic stewardship and inadequate infection control. If Gram-negative organisms, like the *P. aeruginosa*, *Acinetobacter baumannii*, *K. pneumoniae,* previously sensitive to carbapenems were repeatedly exposed to this class of antibiotics, resistance to the carbapenem group of drugs could perhaps arise from two mechanisms: (1) a genetic change in the organism which renders them resistant; (2) the antibiotic would destroy the sensitive strains but a small minority of inherently resistant strains would be left; these in time would multiply and spread, so that we would in time to come, be left with Gram-negative microorganisms resistant to the carbapenem group of antibiotics. Is there a way to remedy this situation? *An important way is for all hospitals to adopt a carbapenem-sparing antibiotic stewardship program. From the epidemiological point of view, restricting the indications and exposure of carbapenems will perhaps restore their efficacy*.

It is however also possible that the frequent use of a number of broad-spectrum antibiotics other than carbapenems, may ultimately lead to Gram-negative organisms becoming resistant to carbapenems. A clinical report described a group of infections due to *K. pneumoniae* in which 45% of *K. pneumoniae* strains produced ESBLs and 3.3% of *K. pneumoniae* strains carried *Klebsiella producing* carbapenemase-2 (KPC-2) carbapenem hydrolyzing enzymes.[15] The prior antibiotic exposure of patients in whom the KPC-2 enzymes were isolated was now investigated. It was observed that most of these patients had received a β-lactam or fluoroquinolone, but only 20% had received a carbapenem. The overall mortality in these bacteremic patients was 47%. Most isolates were from a single ribotype, suggesting that poor infection control was the mechanism for the spread of resistant pathogens selected by antibiotic pressure.

In a similar study in New York, a resistant *Acinetobacter* strain was related to the selection of this pathogen by the frequent use of cephalosporin.[16]

Similar studies relating to carbapenem resistant *P. aeruginosa* or carbapenem resistant *Stenotrophomonas* infection suggest that broad-spectrum agents more so than one specific agent may kill sensitive bacteria and allow pathogens as those stated above to clinically manifest themselves. Another relevant observation is that poor infection control contributes to the spread of resistant strains that have been selected through antibiotic pressure.[16]

CHOICE OF ANTIBIOTICS IN THE ICU

There are several factors that govern the choice of antibiotics to treat infection in the ICU. Many of these factors have already been discussed earlier. For the sake of completeness of this section, they bear brief repetition.

- Empiric antibiotic therapy in severe infections should adequately (in choice and dosage) cover all likely infecting microorganisms. Relevant cultures should be sent prior to empiric therapy. If the infecting microorganisms responsible for an infection is known, antibiotic therapy should be directed solely against that microorganism. A single appropriate antibiotic invariably suffices.
- The choice of antibiotic or antibiotics should not only consider efficacy but also the prevention of further antibiotic resistance.
- Community acquired infections generally need less powerful antibiotics compared to nosocomial infections, except when a community acquired infection is fulminant and life-threatening.
- It is crucial to know the microbiological flora in a particular ICU, the incidence of different organisms as gauged from cultures obtained from infected secretions and the

prevailing antibiotic sensitivity to each of these organisms. The organisms involved in each of the nosocomial infections should be noted as also their antibiotic sensitivity.

- The antibiotic or antibiotics chosen should not only be effective but be least toxic. For this the hepatic and renal function of the patient should be given due consideration.
- The pharmacokinetics of the antibiotic chosen should allow penetration and concentration of the antibiotic at the infected site.
- The cost of antibiotic therapy should also be taken into consideration, particularly in developing countries. It is positively obscene in a poor country to have a patient spend a fortune on very expensive drugs when a simple cheaper drug has the same or even better effect.
- Though it is best to use a single antibiotic, critically ill patients who require prompt empiric therapy, and infections which are invariably polymicrobial (as for example, severe abdominal sepsis), will require a combination of antibiotics. It must however be remembered that multi-drug antibiotic therapy is an important cause of increased antibiotic resistance.
- Finally, patient risk stratification helps in the choice of antibiotic therapy when the infecting microorganisms are unknown. The antibiotic policy may differ in different ICUs. The antibiotic policy or stewardship in our ICU depending both on the antibiogram observed and patient risk stratification is given below. We have stratified patient risks into Type I, Type II, Type III and Type IV.

13

Type I

Admitted to the ICU with a community acquired infection—

- No contact with health care system prior to admission.
- No prior antibiotic use in the previous 30 days.
- Patient young with no significant comorbidity.

Preferred Choice of Empirical Antibiotic Therapy

- IV Amoxicillin Clavulanate.
  or
- IV Ceftriaxone.

Note: Macrolides may be added when suspecting a respiratory tract infection.

Type II

- Contact with health care system (e.g. recent hospital admission or stay in nursing home or on dialysis program).
- Recent antibiotic therapy (within 90 days).
- Patients more than 65 years old with one or more significant comorbidities (involving lung, heart, kidney, liver).

Preferred Choice of Empirical Antibiotic Therapy

- Piperacillin tazobactam +/– macrolide (if respiratory tract infection suspected).
- If culture is positive for ESBL enterobacteriaceae, continue treatment as per sensitivity report (avoid broad spectrum antipseudomonal drugs).
- If cultures are negative for ESBL, de-escalate and treat as in Type I risk.
- If culture shows *P. aeruginosa*, *Acinetobacter*, MRSA escalate and treat as in Type III risk.

Type III (Nosocomial Infection or Fulminant Life-Threatening Community Acquired Infection)

- Severe infection or hospitalization in ICU for 5–7 days prior to infection.
- Infection following major invasive procedure.
- Recent, multiple antibiotic therapy.
- Patient more than 65 years, multiple comorbidities or immunocompromised.
- A community acquired infection which appears fulminant, life-threatening (irrespective of age or other associated factors).

Preferred Choice of Empirical Antibiotic Therapy

- Imipenem/Meropenem/Doripenem/Piperacillin tazobactam/cefoperazone sulbactam + aminoglycosides.
- Add linezolid or vancomycin only if MRSA infection is prevelant in the ICU or in community acquired infections.

Type IV

Type III patients with severe nosocomial infection or patients with fulminant community acquired infection, who run fever and remain very ill in spite of 3 days of adequate antibiotics as stated under type III + have one or more of the following risk factors for invasive fungal infections—

- Total parenteral nutrition (TPN), hemodialysis, immunosuppressed or immune-deficient, major abdominal surgery, diabetes, cirrhosis of the liver, multifocal fungal colonization, use of corticosteroids.

Empiric Antifungal Treatment is Advised

- If no prior exposure to azoles and hemodynamically stable, use fluconazole.
- If prior exposure to azoles and hemodynamically stable, use echinocandins/liposomal amphotericin B.
- Prior exposure to azoles and hemodynamically unstable, use echinocandins/liposomal amphotericin B.
- If *Aspergillus* suspected, start voriconazole.
- Continue as above, if culture shows no growth. If culture shows *Candida albican* sensitive to fluconazole, de-escalate to fluconazole (also see Chapter Invasive Fungal Infections in the ICU).
- If culture reports show susceptible *Pseudomonas*/*Acinetobacter,* continue piperacillin-tazobactam + aminoglycoside for 5 days and then continue piperacillin-tazobactam alone for the next 5–7 days.
- If culture shows non-ESBL enterobacteriaceae or methicillin-sensitive *Staphylococcus aureus* (MSSA) or *Streptococcus*—de-escalate and treat as Type I.

Table 1: Antibiotics of choice for commonly seen Gram-positive cocci and bacilli in the intensive care unit

Organisms	*Drug of first choice*	*Alternative drugs*
Gram-Positive Cocci		
• *Staphylococcus aureus* or coagulase-negative *staphylococci*		
– Penicillinase forming	Penicillinase-resistant, e.g. Cloxacillin, Nafcillin	1st or 2nd generation cephalosporin, vancomycin, ciprofloxacin, ampicillin-sulbactam, amoxicillin-clavulanic acid
– Methicillin-resistant	Vancomycin	Teicoplanin, linezolid, clindamycin, daptomycin, ceftaroline
• β-*hemolytic streptococci*		
– *Streptococcus pneumoniae* (penicillin sensitive)	Penicillin G, ampicillin	First, second, third generation cephalosporins, vancomycin, clindamycin, amoxicillin + clavulanic acid
– Penicillin resistant	Ceftriaxone	Levofloxacin, ertapenem, vancomycin, meropenem, cepefime, linezolid, clindamycin
Gram-Positive Bacilli		
• *Clostridium difficile*	Vancomycin (oral)	Metronidazole (oral), nitazoxanide
• *Clostridium tetani*	Penicillin G	Clindamycin, imipenem, meropenem

If culture shows—

- Multi-drug resistant *Acinetobacter,* start colistin—many prefer a combination of colistin + carbapenem (given as an extended infusion for 3 hours).
- Multi-drug resistant *P. aeruginosa*/*Klebsiella* – colistin + antipseudomonal β-lactam-β-lactamase inhibitor or carbapenems (extended 3 hours infusion).
- Vancomycin-resistant enterococcal (VRE), start linezolid/daptomycin.
- If for any reason a fungal infection is strongly suspected even though blood for fungal cultures are negative, treat for fungal infections as stated earlier under Type IV.

Risk stratification and use of appropriate antibiotics is undoubtedly not uniform for all ICUs. Each unit must decide on its own risk stratification and choice of antibiotics as per the prevalent microorganisms and the antibiogram in relation to these microorganisms.

A continuous surveillance of the possible changing 'flora' and changing susceptibility to various antibiotics is important to allow a modification of antibiotic choice in the ICU. This indeed is the essence of antibiotic stewardship.

TREATMENT OF PROVEN MULTI-DRUG RESISTANT *ACINETOBACTER BAUMANNII* INFECTION

The *Acinetobacter baumannii* is a dangerous Gram-negative organism often resistant to most available classes of antimicrobial agents. Once it gains entry into an ICU, it can wreak havoc among patients and is difficult to eradicate. The organism can persist within the environment of the ICU for weeks, being present on walls, tables, curtains, beds, respiratory and other equipment; it can contaminate water, disinfectants, monitors, thermometers, key pads of computers, laptops and the clothing of medical, paramedical and nursing personnel.[17]

This organism is often increasingly resistant to all classes of antibiotics, yet by and large so far has retained its sensitivity to colistin.

The optimal dose of colistin is unclear due to a lack of accurate pharmacokinetic and pharmacodynamic information. Studies have advocated the use of a loading dose of 9 million units IV and a maintenance dose of 4.5 million units IV 12 hourly or 3 million units IV 8 hourly in critically ill patients.[18]

In 2006, Li et al.[19] reported the phenomenon of hetero-resistance to colistin in multi-drug resistant *Acinetobacter* clinical isolates. Due to a resistant subpopulation, significant regrowth was observed within 24 hours following the initial killing (<2 hours) of the organisms by colistin. This suggests that the concentration of colistin in the blood achieved by the recommended dose of colistin may not be able to eradicate the more resistant subpopulation. The clinical application arising from the above microbiological findings is the recommendation not to use colistin alone against *Acinetobacter baumannii* infection but to combine it with another antimicrobial agent. The combination generally preferred is colistin + carbapenems, or colistin + piperacillin-tazobactam given as extended infusions.

Tigecycline can also act against *Acinetobacter baumannii* though its clinical efficacy remains controversial. The drug is bacteriostatic and resistance to the drug can occur during therapy. Tigecycline should not be used as monotherapy and is best used in combination with colistin. Tigecycline has low serum C_{max} values and should be avoided in bacteremia.[20]

Sulbactam In patients having sulbactam susceptible *Acinetobacter baumannii* infections, sulbactam should be the drug of choice, again combined with colistin.[5]

Rifamycin has an antibacterial activity against *Acinetobacter baumannii*. It is not used alone but in combination with another drug—preferably with colistin.[5]

Minocycline Minocycline also may have a role in minocycline susceptible *Acinetobacter baumannii* infections again in combination with another drug. There are very few clinical studies on this subject.[5]

A series of recently reportedly peptides have shown strong anti-bacterial activity against multi-drug resistant

Table 2: Antibiotics of choice for commonly seen Gram-negative cocci and bacilli in the intensive care unit

Organisms	*Drug of first choice*	*Alternative drugs*
Gram-Negative Cocci		
Neisseria meningitidis	Penicillin G, ampicillin, ceftriaxone, ceftazidime	Cefepime, meropenem
Gram-Negative Bacilli		
• Bacteroides fragilis	Piperacillin + tazobactam, any carbapenem, tigecycline	Clindamycin, metronidazole, ampicillin-sulbactam, amoxicillin-clavulanic acid
• *Enterobacter* sp.	Cefepime	Aztreonam, any carbapenem
• *Escherichia coli*	Third generation, cephalosporins	Piperacillin + tazobactam, Aminoglycosides, carbapenem
• *Pseudomonas aeruginosa*	Antipseudomonal, penicillins or ceftazidime	Ciprofloxacin or aztreonam, carbapenem + aminoglycosides, colistin + carbapenem
• *Klebsiella pneumoniae*	Ceftriaxone, cefoperazone, ceftazidime	Piperacillin, ampicillin-sulbactam, carbapenem
• Haemophilus influenzae	Cefuroxime, ceftriaxone, ceftazidime	Piperacillin + tazobactam, levofloxacin, azithromycin
• *Proteus* sp.	Cefotaxime, ceftriaxone, cefepime	Aminoglycosides, quinolones, aztreonam, meropenem
• Acinetobacter	Carbapenems	Colistin + Carbapenem/Sulbactum/Tigecycline

Acinetobacter baumannii. It may take some time for these new drugs to be carefully tried before use.

Table 1 lists the antimicrobial of choice for commonly encountered Gram-positive cocci and bacilli and Table 2 lists the antimicrobial of choice for commonly encountered Gram-negative cocci and bacilli.

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MODE OF ACTION OF ANTIMICROBIAL AGENTS

Antimicrobial agents may be either bactericidal or bacteriostatic. Bactericidal agents kill microorganisms, whereas bacteriostatic agents prevent multiplication of the microorganisms, only when present within them. A critically ill patient in the ICU is often at a special disadvantage because of poor phagocytic function of the macrophages. There is also at times poor antibody function, as compared to less ill patients. Bactericidal agents should therefore be preferred; yet in many situations, bacteriostatic agents act just as well.

The mechanism of action of antimicrobial agents on microorganisms varies and may take the following forms—

- Interference with cell wall synthesis. This is the main mode of action of penicillins, cephalosporins, carbapenems, monobactams and vancomycin.
- Interference with cell membrane synthesis as with polymyxins and amphotericin B.
- Prevention of DNA replication, e.g. quinolones, rifampicin and metronidazole.
- Interference with protein synthesis as seen with chloramphenicol, tetracyclines, erythromycin, clindamycin, aminoglycosides and fusidic acid.
- Folic acid antagonists, e.g. sulfonamides, trimethoprim and their combinations.

The different modes of action of important antimicrobial agents have been illustrated in Figure 2.

The remaining part of this chapter deals very briefly with antibiotics used for serious infections in the ICU. Treatment for fungal infections has been discussed separately.

PENICILLINS

Penicillin G

In the ICU, this cheap and extremely effective antibiotic is used against acute pneumococcal infection, streptococcal infection, meningococcal infection and infections by Gram-positive bacilli—chiefly the clostridia. It is no longer used for treating *Staphylococcus* infections, as these strains are resistant to the drug. In fulminant infections in adults, the dose is 4,000,000 units intravenously (IV) 4 hourly.

Ampicillin

Ampicillin is a broad-spectrum penicillin with a significant spectrum of activity against Gram-negative bacilli. It is also nearly as effective as penicillin G against Gram-positive and Gram-negative cocci, and Gram-positive bacilli. It can therefore be used in place of penicillin G to treat fulminant infections mentioned under penicillin G. It is the drug of choice for infections due to *Enterococci*. Ampicillin and aminoglycosides form an extremely effective combination against *Enterococci*, as these drugs are synergistic against these organisms. The chief drawbacks of ampicillin are: (1) susceptibility to β-lactamase produced by *Staphylococci* and Gram-negative bacilli—most strains of *S. aureus* and more than 50% of *Escherichia coli* are ampicillin-resistant; (2) the occurrence of hypersensitivity reactions and (3) gastrointestinal side effects. These are similar to those observed with penicillin G and are briefly described below.

In fulminant streptococcal or in other fulminant infections as in pneumococcal or meningococcal meningitis, the dose of ampicillin is 2 g IV 4 hourly, i.e. 12 g/day. In less fulminant cases, 1 g IV 4 hourly suffices.

Anti-Staphylococcal Penicillins: Cloxacillin, Flucloxacillin and Methicillin

These are not destroyed by penicillinases, i.e. by β-lactamase enzymes. They are therefore most useful against *S. aureus*, most of which produce penicillinase. They are however

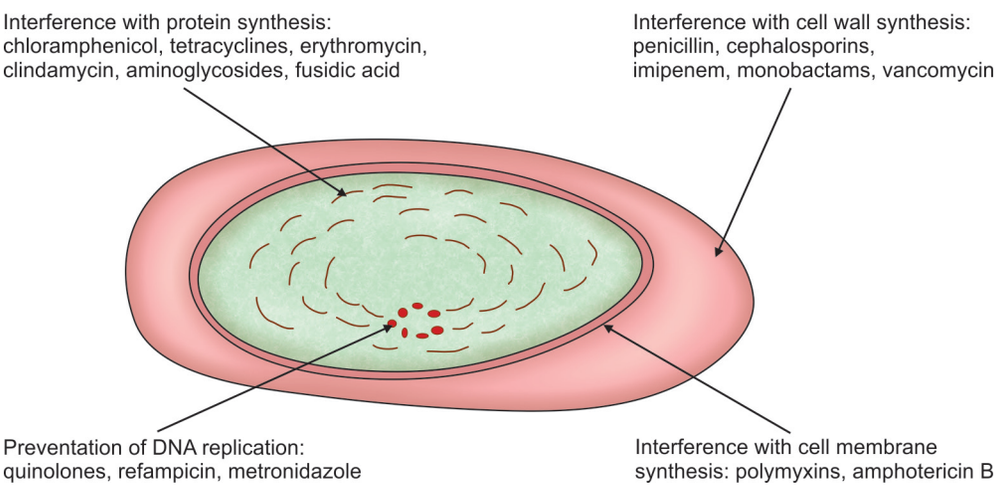

Fig. 2: Modes of action of important antimicrobials

less effective against other Gram-positive organisms, and inconsistently effective against *Staphylococcus epidermidis*. There is also an in vitro cross-resistance and cross-sensitivity between these three drugs, as also between these drugs and the cephalosporins.

Cloxacillin is only reserved for methicillin-sensitive staphylococcal infections in our unit; the dose in serious infections being 1 g IV 4 hourly. The incidence of MRSA is slowly increasing. In some other hospitals, notably those treating cancer patients, the incidence of MRSA is high.

Side Effects of Penicillins

The penicillins described above occasionally produce reactions. Antibody-mediated hypersensitivity reactions in rare instances may cause fatal anaphylaxis. Though a skin sensitivity test is mandatory before starting penicillin therapy, a negative skin test does not exclude the possibility of anaphylaxis. Other antibody-mediated hypersensitivity reactions include fever, urticaria, serum sickness and nephritis. Non-antibody-mediated reactions often occur in association with viral (notably Epstein-Barr virus) infections and take the form of fever with a measles-like rash.

Very large doses of penicillin, particularly in the presence of renal failure, may cause seizures, hemolytic anemia, neutropenia and thrombocytopenia.

Penicillins and β-Lactamase Inhibitors

The major mechanism of β-lactam resistance seen in both Gram-positive and Gram-negative infections is due to production of β-lactamase. The three currently available β-lactamase inhibitors are clavulanic acid, tazobactam and sulbactam.[1,2] The β-lactam-β-lactamase inhibitor, antibiotic combinations available are piperacillin-tazobactam, ticarcillin-clavulanate, ampicillin-sulbactam and amoxicillin-clavulanic acid. The last two combinations are effective against β-lactamase producing strains of *S. aureus*, *Haemophilus influenzae* and *Bacteroides fragilis*.[1,2]

Piperacillin tazobactam and ticarcillin-clavulanic acid are used against ESBL producing Gram-negative infections—in particular infections due to *P. aeruginosa* and *K. pneumoniae*.

Unfortunately, many Gram-negative organisms are now showing a steadily increasing resistance to piperacillin tazobactam and ticarcillin-clavulanic acid, particularly in ICU patients. In suspected Gram-negative infections, where the exact organisms causing infection are undetermined, empiric therapy with piperacillin-tazobactam + aminoglycoside or ticarcillin-clavulanic acid + an aminoglycoside is frequently used. The above combination is often prescribed in patients with intra-abdominal sepsis, pelvic suppuration, acute biliary infection as in cholangitis and cholangitic abscess. The dose of piperacillin-tazobactam is 4.5 g IV 8 hourly and of cefoperazone + sulbactam 3.1 g IV 8 hourly. Piperacillin-tazobactam should be used with caution in patients with renal and hepatic dysfunction.

AMINOGLYCOSIDES

These are extremely useful against Gram-negative bacilli including *Klebsiella* and *P. aeruginosa*. The aminoglycosides commonly used are gentamicin, tobramycin and amikacin. In severe fulminant Gram-negative infections, an aminoglycoside is always combined with another suitable antibiotic—either a third generation cephalosporin or piperacillin-tazobactam. Gram-negative infections in neutropenic patients should also preferably include an aminoglycoside in the therapeutic regime. The degree of resistance of Gram-negative organisms to aminoglycosides varies in different units. In our unit gentamicin-resistant organisms are frequently observed. We therefore prefer to use amikacin. Tobramycin offers no special advantage over gentamicin or amikacin.

It is important to bear in mind that ESBL producing Gram-negative organisms that are resistant to penicillins and first, second, third generation cephalosporins often also encode a gene which confers resistance to aminoglycosides as well.

Dosage

Aminoglycoside dosing is based on bodyweight. Only a small fraction of the aminoglycoside is distributed in adipose tissue, so that ideal bodyweight should be taken into consideration for estimating dosage in obese individuals as this could prevent overdosing. However, dosing based on ideal bodyweight may result in over dosage in patients who are underweight. It has been suggested that one can compare the ideal and actual bodyweight of each patient and use the lower of the two weights to determine the aminoglycoside dose.[3]

Once-Daily Dosing

The effect of aminoglycoside is concentration-dependent, higher concentration in the blood stream and tissues producing a greater bactericidal effect.[3] This is the rationale for using a single daily dose of the drug rather than divided dose regimes. There is no incontrovertible proof that once-daily dosing is more effective with regard to ultimate outcome than the divided dose regimen, though once-daily dosing continues to be preferred for being less time consuming and less costly. Efficacy and toxicity are probably the same as with divided dose regime.

In patients with renal dysfunction the dosage needs to be modified as per the creatinine clearance. This can be achieved by either decreasing the strength of the dose and/or an increase in the dosing interval. The dosing adjustment depending on creatinine clearance is given in the Table 3.

Toxic Effects

The major toxic effects of aminoglycosides are nephrotoxicity causing renal failure, and toxicity to the eighth cranial nerve causing deafness.[4-6]

The nephrotoxicity is due to the action of the aminoglycosides on the renal tubules. It is a very important primary cause or a contributory cause of renal failure in patients

Table 3: Aminoglycoside dosing by creatinine clearance

Cr/Cl (mL/min)	*Gentamicin/ Tobramycin (mg/kg)*	*Amikacin*	*Dosing interval*
>100	5.0	15.0	24 hours
70	4.0	12.0	↓
50	3.5	7.5	↓
40	2.5	7.5	48 hours
20	4.0	7.5	↓ 72 hours
10	3.0	4.0	↓
HD	2.0	5.0	96 hours

Abbreviations: Cr/Cl, creatinine clearance; HD, hemodialysis.
Source: Adapted from Turnidge J. Pharmacodynamic and dosing of aminoglycosides. Inf Dis Clin N Am. 2003.17:503-28.

in the ICU. Renal failure is generally (though not always) of the nonoliguric variety, the patient excreting more than 1,200 mL/day, yet showing a progressive rise in the serum creatinine. Both gentamicin and amikacin are equally nephrotoxic. Nephrotoxicity is related to drug levels in the blood. The likelihood of toxicity is thus related to the duration of time that the trough serum levels exceed 2 μg/mL for gentamicin, and 10 μg/mL for amikacin.[7] The rise in serum creatinine occurs after 5–7 days but can occur earlier in the presence of biliary obstruction,[6] or if there is some degree of renal insufficiency to start with. The use of furosemide and the presence of hypovolemia potentiate aminoglycoside nephrotoxicity.[8] Aminoglycosides are best omitted if renal toxicity is apparent from a rising serum creatinine level. Acute renal failure generally resolves within a week; rarely, it may take much longer to resolve, and the patient may then need to be supported by dialysis.

Early signs of renal toxicity include a fall in the urine output, proteinuria, and the presence of casts in the urine. These signs are however nonspecific and may be due to other causes operating in very ill patients in the ICU.

Ototoxicity from aminoglycosides results in nerve deafness and is dose-related. The nerve deafness is enhanced by the use of furosemide.[7,8] Rarely aminoglycosides potentiate neuromuscular blockade. In clinical practice, this is only observed in patients with myasthenia gravis, or in those being given muscle relaxants.

Prevention of toxic effects of aminoglycosides is helped by maintaining a normal intravascular volume and by the discriminate use of furosemide. Aminoglycosides should not generally be continued once the cultures are negative. In patients where renal failure is a likely hazard, one often prefers to use a safer antibiotic.

GLYCOPEPTIDES

Vancomycin[9]

Vancomycin is the drug of choice for MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE) infections and for serious infections in patients allergic to penicillin. The drug is also used for penicillin resistant pneumococcal meningitis and pneumonia. It also forms a second-line therapy for most Gram-positive infections. When used against *Enterococci*, the drug should be given together with an aminoglycoside.

There are increasing numbers of reports related to MRSA strains showing reduced susceptibility to vancomycin. The emergence of MRSA strains with reduced vancomycin susceptibility has limited treatment options and increased the incidence of treatment failure. Also, the upward drift in the MIC for vancomycin in MRSA is associated with an increased risk of clinical treatment failure.

Vancomycin resistant *Enterococci* have been increasingly reported. The gene encoded within *Enterococci*, which confers resistance to vancomycin, can be transferred to the *S. aureus* so that problem of vancomycin resistant staphylococci in time to come may become formidable.

Dosage

The dose is 1 g 12 hourly IV. The drug is effective when used orally in a dose of 125–250 mg four times a day for *Clostridium difficile* infections.

Side Effects

The major side effects are on the kidneys and on the eighth nerve. Renal insufficiency and ototoxicity are thus to be watched out for. The dose should be appropriately reduced on the basis of the creatinine clearance test. Drug levels should be monitored in the presence of impaired renal function. If the drug is given as a bolus, or even otherwise, the drug can cause a severe erythematous rash, flushing and transient hypotension (Red Man Syndrome).

Teicoplanin

Teicoplanin is a new glycopeptide, which has a similar spectrum to vancomycin. Its main use is again MRSA and MRSE infections. It is believed to be less toxic than vancomycin.

Dosage

Adult Initially, 6 mg/kg on first day, followed by 3 mg/kg per day. Severe infection—6 mg/kg every 12 hour for the first 3 doses followed by 6 mg/kg per day. Doses may be given via intramuscular injection, IV bolus or IV infusion over 30 minutes.

Renal impairment Usual dose to be given for first 3 days, thereafter adjust dose according to creatinine clearance.

Creatinine clearance rate (mL/minute)	Dosage recommendation
40–60	1/2 initial dose given daily or initial dose every 2 days
Less than 40	1/3 initial dose given daily or initial dose every 3 days

Side Effects

It can cause both nephrotoxicity and ototoxicity.[10] The dose should be suitably reduced in patients with renal insufficiency. Thrombocytopenia can occur with higher doses.

β-LACTAM ANTIBIOTICS

A number of β-lactam antibiotics have been in use against resistant facultative Gram-negative bacilli. Of these, the commonly used ones are the third and fourth generation cephalosporins.

Third Generation Cephalosporins[11]

Cefotaxime, ceftazidime, ceftriaxone and cefoperazone are the third generation cephalosporins, which have been in frequent use against serious Gram-negative infections in the ICU for the last several years. They penetrate well into the CSF, and are therefore the drugs of choice in Gram-negative bacterial meningitis. Ceftazidime provides a wider cover (which includes *Pseudomonas*) and is to be preferred particularly for empiric therapy against Gram-negative bacterial meningitis. Gram-negative nosocomial infections in the ICU, as also infection of unknown origin in neutropenic patients, warrant the use of a third generation cephalosporin together with an aminoglycoside or ciprofloxacin. Cefotaxime is useful against Gram-negative organisms particularly *Klebsiella*, but lacks activity against *Pseudomonas*. Ceftazidime, on the other hand, has the greatest activity against *P. aeruginosa*, and some other *Pseudomonas* species. Cefoperazone sulbactam also has antipseudomonal activity and has significant activity against Gram-positive organisms including *Staphylococci*. Third generation cephalosporins are poorly active against *B. fragilis*, and display no activity against *Enterococci*, *Listeria*, and methicillin-resistant *Staphylococci*.

The above description of the use of third generation cephalosporins in relation to the treatment of Gram-negative infection unfortunately does not hold true since the growing presence of ESBL producing organisms. ESBLs renders Gram-negative organisms resistant to all penicillins, all first, second, third generation cephalosporins and to aztreonam.

The third generation cephalosporins offer two important advantages—

1. *Good tissue penetration* Penetration into the CSF has already been commented upon. Ceftriaxone and cefoperazone also reach high concentrations in the bile and may therefore be of special value in the treatment of severe cholangitis and cholangitic abscesses.
2. *Reduced nephrotoxicity* Cefotaxime, ceftriaxone and cefoperazone have little or no renal toxicity. Cefoperazone can thus be continued without any reduction in the dose in patients with renal failure. The dose of ceftazidime however needs to be reduced in patients with renal insufficiency; the degree of reduction is dependent on the serum creatinine levels and on creatinine clearance values.

Side Effects

The major side effect noticed in the ICU is the occurrence of reversible neutropenia in 10% of patients. This may cause confusion in the management of neutropenic patients. A slight rise in the liver enzymes is occasionally encountered. Prolonged prothrombin time and platelet dysfunction causing bleeding can sometimes occur, particularly with cefoperazone. Rarely, a positive Coombs test is related to cephalosporin therapy.

Dosage

Cefotaxime is administered in a dose of 1–2 g 6 hourly. The dose of ceftazidime is 1–2 g 12 hourly. Ceftriaxone and cefoperazone have much longer half-lives, and have the added advantage of a once a day dosing of 2 g IV. In fulminant infections the dose can be increased to 4 g daily.

Fourth Generation Cephalosporins[12]

Cefepime and Cefpirome are the fourth generation cephalosporins. They have good activity (similar to that of ceftazidime), against Gram-negative pathogens, including Enterobacteriaceae and *P. aeruginosa*. Some strains of enterobacter, citrobacter and serratia resistant to ceftazidime, aztreonam are susceptible to cefepime and cefpirome. They are also active against Gram-positive organisms (*Streptococcus pneumoniae*, *Streptococcus pyogenes* and MRSA)—activity similar to cefotaxime but better than ceftazidime. Like other cephalosporins they do not have activity against anaerobes. Compared to other second and third generation cephalosporins, they have lower affinity for β-lactamases and are not inducers of chromosomal β-lactamases.

Indications

They are used in Gram-negative infections, as in nosocomial pneumonia, urinary tract infections, febrile neutropenia, intra-abdominal infections (along with metronidazole).

Dosage

- Cefepime 1–2 g 12 hourly, 2 g 8 hourly, IV.
- Cefpirome 1–2 g 12 hourly, IV.

Both drugs require dosage adjustment in patients with renal dysfunction.

Side Effects

Side effects are similar to other cephalosporins. Cefpirome interferes with serum creatinine estimation by Jaffe's method. Hence falsely elevated serum creatinine levels will result, though blood urea nitrogen remains unaffected. Hence, cefpirome should be administered after blood sample collection or the high-performance liquid chromatography (HPLC)/enzymatic method should be used for estimating serum creatinine.

QUINOLONES

Ciprofloxacin

Ciprofloxacin has the following advantages—

- An excellent activity against Gram-negative organisms, particularly against *Bacillus typhosus*, Salmonella infection and *Pseudomonas*. It is therefore a useful alternative to aminoglycosides when combined with either piperacillin or ceftazidime or cefpirome in the treatment of *Pseudomonas* infections.
- Activity against MRSA and epidermidis. However, strains of MRSA are now becoming increasingly resistant to ciprofloxacin.
- Good tissue penetration, particularly in bones, lungs, bronchi, the hepatobiliary system, gut, prostate and the urinary tract. Penetration into the CSF is however poor. It is therefore useful against Gram-negative infections involving the above sites, particularly in severe osteomyelitis.

Ciprofloxacin lacks activity against *B. fragilis* and many non-aeruginosa species of *Pseudomonas*.

Again, it must be mentioned that ESBL producing Gram-negative organism are often found to be resistant to ciprofloxacin. There is also an increasing resistance particularly of *P. aeruginosa* and *K. pneumoniae* to ciprofloxacin though the degree of resistance will vary in different ICUs.

Dosage

In fulminant infections, it is administered intravenously in a dose of 200 mg 12 hourly. Once the infection is under good control, it is given orally in a dose of 500–750 mg twice a day.

Side Effects

Gastrointestinal disturbances are frequent. Skin rashes and transient gouty pains involving the fingers may be observed. A transient elevation in liver enzymes, and rarely in serum creatinine, may occur. The dose may need to be reduced in patients with renal insufficiency. Central nervous system excitation may take the form of headache, confusion and seizures. Serious but very rare side effects include anaphylactoid reactions that may cause death and possibly a hemorrhagic vasculitis.[13]

The drug is best avoided (unless absolutely necessary) in children, and pregnant and lactating women.

Newer Fluoroquinolones[14]

The newer fluoroquinolones include ofloxacin, levofloxacin (L-isomer of ofloxacin), gatifloxacin, moxifloxacin. These drugs are active against Gram-negative bacilli, including *Salmonella*, *B. typhosus*, *Shigella*, *H. influenzae* and *Pseudomonas* strain. However, among fluoroquinolones, ciprofloxacin has the highest activity against *Pseudomonas*. While ciprofloxacin and ofloxacin are also active against mycobacteria, the other fluoroquinolones are active against *mycoplasma*, *chlamydia* and *legionella*. For serious Gram-negative infections in the ICU, we have restricted the use of quinolones to ciprofloxacin and ofloxacin. They are invariably used in combination with a third generation or fourth generation cephalosporin or with piperacillin. Ciprofloxacin or ofloxacin is the drug of choice in fulminant *B. typhosus* infection. However, resistance of *B. typhosus* (Brucella) to these drugs has progressively increased so that the drug of choice against *Salmonella* infections today is ceftriaxone.

Dosage

The intravenous dose of ofloxacin is 200–400 mg 12 hourly. Gatifloxacin is given intravenously—400 mg once daily. The intravenous dose of levofloxacin and moxifloxacin is 500–750 mg once daily and 400 mg once daily respectively.

Side Effects

The side effects of the newer quinolones are by and large similar to those of ciprofloxacin.

MONOBACTAMS[15,16]

Aztreonam

This is a narrow spectrum antibiotic to be used exclusively against Gram-negative aerobic organisms. It does not have any activity against Gram-positive organisms and anaerobes. There is synergy reported between aztreonam and aminoglycosides against *P. aeruginosa*. Here again, Gram-negative organism producing ESBL are resistant to aztreonam.

Indications

Intra-abdominal sepsis, urinary tract infections and nosocomial pneumonia.

Dosage

The dose is 1–2 g IV every 6–8 hours. The dosage needs to be suitably adjusted in patients with renal failure.

Side Effects

Side effects are minor. Rarely, a rise in serum liver enzymes and in serum bilirubin have been reported.

LINEZOLID[17,18]

Linezolid is an oxazolidinone group antibiotic. It is bacteriostatic and acts by inhibiting the initiation of protein syntheses. It is predominantly effective against Gram-positive organisms, like MRSA, vancomycin-resistant enterococci, vancomycin-intermediate-resistance *Staphylococcus aureus* and penicillin-resistant pneumococci. It has 100% bioavailability when administered orally.

Linezolid may be associated with improved survival and better clinical cure rate compared to vancomycin in patients with nosocomial pneumonia caused by MRSA.[19] It is perhaps a more suitable alternative to vancomycin in nosocomial infections caused by MRSA particularly in pneumonia. There is however no definite proof of the superiority of linezolid over vancomycin or teicoplanin for other infections.

Dosage

The dose is 600 mg IV or orally every 12 hours.

Side Effects

The drug can cause vomiting, diarrhea and lead to candidal superinfection. Linezolid is a weak monoamine inhibitor and has a potential for interaction with adrenergic drugs. Resistance of organisms to the drug can occur on prolonged therapy; hence the routine use of this antibiotic should be discouraged.

CARBAPENEMS

Imipenem

Imipenem is a carbapenem with the widest antibacterial spectrum of any available antibiotic.[20,21] The drug is inactivated by enzymes in the renal tubule so that the drug cannot achieve high concentration in the urine. This is overcome by combining imipenem with an enzyme inhibitor cilastatin. Imipenem is one of the most expensive antimicrobials in use today. It is active against most clinically important bacteria. It has no activity against *Enterococcus faecium*, *Stenotrophomonas maltophilia*, many strains of *Burkholderia cepacia* and methicillin-resistant *Staphylococci*. Imipenem also inhibits endotoxin release from the Gram-negative bacterial cell wall.[22] It is therefore an extremely valuable drug to treat fulminant, unidentified infections in the ICU, or to treat fulminant infections due to multiple drug-resistant bacteria. It is particularly useful: (1) as empirical treatment of infection in severely immunocompromised patients; (2) in intra-abdominal or pelvic sepsis involving mixed infections with aerobes, anaerobes and enterococci; (3) infections with *Enterobacter* or *P. aeruginosa* resistant to other antibiotics.[13] It probably can be used as a single antibiotic in such patients. When the possibility of methicillin-resistant staphylococcal infection cannot be excluded, it should be combined with vancomycin.

The drug should be used with caution, restraint and circumspection as resistant bacteria are bound to emerge.[20,21] In fact, resistant bacteria have indeed emerged. Gram-negative organism producing carbapenases (metalloenzymes) are resistant to the action of carbapenems.

Dosage

Imipenem is given intravenously in a dose of 500 mg 6 hourly. The dose should be reduced by 50–75% in patients with renal failure.[23]

Side Effects

The main side effects are skin rashes, phlebitis, gastrointestinal symptoms and seizures, particularly in patients with renal insufficiency. Seizure disorders are reported in 1–3% of patients.[23] Patients with a previous history of seizure disorder are more prone to this complication.

Meropenem[15,16]

Meropenem is later carbapenem similar to imipenem. It has the same range of activity against Gram-negative organism and against anaerobes as imipenem.

Dose

The drug is given in a dose of 0.5–1 g 8 hourly in an intravenous infusion.

Side Effects

Incidence of seizures is reported to be less as compared to imipenem. The drug does not affect renal function.

Doripenem[24]

Doripenem is another Group 2 carbapenem with activity similar to meropenem and imipenem. It has the same spectrum of activity and potency against Gram-positive cocci as imipenem. Its Gram-negative activity is similar to that of meropenem except in *P. aeruginosa* where doripenem is twofold more potent than meropenem and imipenem.[25]

Dose

It is administered as 500 mg to 1 g 8 hourly IV. For drug resistant Gram-negative organisms, especially in patients with nosocomial pneumonias, it may be given as a 4-hour infusion.

Side Effects

Headache, nausea, diarrhea and phlebitis are the most commonly reported drug-related adverse events due to doripenem.

Ertapenem[26]

Ertapenem is a group 1 carbapenem that has similar spectrum of activity as imipenem and meropenem except that it does not act against *Pseudomonas* and *Acinetobacter*. It also acts against most Gram-positive bacteria excepting MRSA and *E. faecium*; it has excellent anaerobic activity.

Dose

It is administered as 1 g single dose either intravenously or intramuscularly. The once-daily regimen is attributed to its high protein binding capacity.

Side Effects

Nausea, vomiting and diarrhea may be seen in a small percentage of patients.

Tigecycline

It is the first of the glycyclines, which has an activity against aerobic Gram-negative bacteria and Gram-positive bacteria and anaerobes. The drug is particularly useful for the treatment of surgical wound infections, where both Gram-negative and MRSA are likely pathogens. It has an important role in the treatment of intra-abdominal infections, particularly due to multi-resistant organisms. These include Acinetobacter species, ESBL producing enterobacteriaceae, carbapenamase producing enterobacteriaceae, enterococci, Stenotrophomonas maltophilia. The drug has no action against Ps. aeruginosa and Proteus mirabilis.

Dosage

The dose is 100 mg loading dose followed by 50 mg IV twice daily. The major side effects appear to be dose related nausea and vomiting.

Polymyxin B and Colistin (Polymyxin E)[27]

Polymyxin B and colistin (polymyxin E) are cyclic cationic polypeptides, which act as membrane active agents on the Gram-negative cell wall. Colistin has recently emerged as a salvage drug for the treatment of severe multi-drug resistant Gram-negative infections. Colistin acts as a surface-active agent, and creates holes in the cell membrane of Gram-negative bacteria and disrupts them. It also binds to the lipopolysaccharide unit of the Gram-negative bacterial cell wall and blocks its endotoxic activity. Polymyxins selectively act on Gram-negative bacteria but are intrinsically resistant to *Providencia*, *Burkholderia*, *Morganella*, *Moraxella*, *Brucella*, *Edwardsiella*, *Vibrio*, *Aeromonas* and *Helicobacter* species. They also do not possess any activity against Gram-positive bacteria and anaerobes. In critically ill patients, it has been observed that after the initial rapid kill (<2 hours), there is substantial regrowth of organisms within 24 hours even when the dose of colistin is 64 times the minimum inhibitory concentration of *Acinetobacter*. This regrowth is due to resistant subpopulations and is termed as heteroresistance. Thus, polymyxins should never be used as monotherapy but always in combination with either imipenem, β-lactams, fluoroquinolones, tigecycline, minocycline or rifampicin. Complete cross-resistance is observed between the two polymyxins.

Dose

To start with, the prescribed dose is 1–2 million International units (IU) thrice daily. Recently, pK–pD studies conducted in critically ill patients have shown that colistin concentrations in vivo are below the MIC breakpoints (2 mg/L) even after the first few doses of the currently used dosing regimen. This amounts to a delay in starting appropriate treatment in the critically ill patients and is associated with increased mortality. Therefore, loading of up to 9 million IU and maintenance dosing (4.5 million IU twice daily) regimens have been recommended for colistin in combination with another antimicrobial agent. In patients with Gram-negative pulmonary infection, one to two million units of the daily dose can be given by nebulization.

Side Effects

- Nephrotoxicity and neurotoxicity.

NEWER ANTIBIOTICS

Daptomycin[28]

This drug is a lipopeptide active against Gram-positive cocci and MRSA. It is active against resistant and susceptible isolates of *S. aureus* and *enterococci*. The drug has been recently approved for the treatment for complicated skin and soft tissue infections. Daptomycin should not be used in the treatment of pneumonia as it is degraded by surfactant present in the lung. Its main use in limited to skin infections, bacteremia and endocarditis. It is given in a once-daily dosing of 4 mg/kg IV. The drug has a good safety profile except that it has been reported to cause rhabdomyolysis.

Quinupristin/Dalfopristin[29]

This drug is a streptogramin antibiotic. The drugs are present in a fixed 30:70 ratio and are synergistic. It is active against Gram-positive bacteria including VRE and MRSA. It is a bacteriostatic drug. It does not have activity against *Enterococcus faecalis*.

Dosage

The dose is 7.5 mg/kg IV 8 hourly for seriously ill patients to be administered preferably through a central vein, as local reactions may occur with use through peripheral veins.

Side Effects

The drug causes myalgias and arthralgias in up to 10% of patients.

Ceftobiprole and Ceftaroline[30]

They belong to the fifth generation of broad-spectrum cephalosporins with potent bactericidal activity against MRSA and penicillin resistant streptococcal pneumonia. The drug has a strong affinity for penicillin binding proteins of most Gram-negative and Gram-positive pathogens and is resistant to β-lactamase. It is being approved for use in patients with pneumonia and complicated skin and soft tissue infections (SSTIs).

Dalbavancin, Telavancin and Oritavancin[31]

These are bactericidal (inhibit cell wall synthesis) lipoglycopeptides with activity against Gram-positive bacteria. In addition to inhibiting cell wall synthesis, telavancin and oritavancin are also able to disrupt bacterial

membrane integrity and increase membrane permeability while oritavancin also inhibits RNA synthesis. The half-life of dalbavancin ranges from 147 hours to 258 hours, which allows for once-weekly dosing. The half-life of oritavancin of 393 hours may allow for one dose per treatment course, while telavancin requires daily administration. They are especially useful in the treatment of vancomycin resistant organisms. Clinical trials involving patients with complicated skin and skin structure infections (cSSSIs) have demonstrated that all three agents are equally efficacious. Telavancin was approved in 2009 for the treatment of complicated skin and skin structure tissue infections. Oritavancin and dalbavancin are still under clinical trials.

Dose

- Telavancin 600 mg 12 hourly daily.

Side Effects

The most common adverse effects reported are nausea, diarrhea, constipation, fever, taste disturbances and injection site reactions.

DRUG INTERACTIONS

Most ICU patients receive multiple drugs. The possibility and the potential for drug interactions are therefore very significant and should always be considered. Table 4 provides

Table 4: Modifications in dose and frequency of administration of important antimicrobial agents in patients with hepatic or renal dysfunction

Antibiotics	*Interval between doses with various creatinine clearances (renal failure)*			*Dose altered by dialysis*		*Dose in hepatic failure*
	Normal (50–80 mL/min)	*Moderate (10–50 mL/min)*	*Severe (<10 mL/min)*	*Hemodialysis*	*Peritoneal dialysis*	
1. Penicillin	4 hr	NC	1 MU/6 hr	1 MU/6 hr	No	NC
2. Ampicillin	1g/4 hr	1g/8 hr	1 g/12 hr	1 g	1 g	NC
3. Cefotaxime	2 g/6–8 hr	1 g/6 hr	1 g/12 hr	1 g	1 g	NC
4. Ceftazidime	2 g/8 hr	1g/24 hr	0.5 g/24 hr	1 g	0.5 g	NC
5. Piperacillin + tazobactam	3.375 g/6 hr	3.375 g/6 hr	2.25 g/6 hr	0.75 g	NC	NC
6. Imipenem	0.5 g/6 hr	0.5 g/8 hr	0.25 g/12 hr	0.25 g	Yes	NC
7. Meropenem	1 g/12 hr	0.5 g/12 hr	0.5 g / 24 hr	0.5 g	0.5 g	NC
8. Gentamicin*	2.5 mg/kg /24 hr	2.5 mg/kg/48 hr	1.5 mg/kg/48 hr	1 mg/kg	0.5 mg/kg	NC
9. Amikacin*	8 hr	7.5 mg/kg/48 hr	3.75 mg/kg/48 hr	7.5 mg/kg	3.75 mg/kg	NC
10. Ciprofloxacin	0.4 g/8–12 hr	0.4 g/12 hr	0.4 g/24 hr	0.2–0.4 g	0.2–0.4 g	NC
11. Vancomycin*	0.5 g/12 hr 6–12 hr	0.5 g/12 hr	0.5 g/24 hr	No	No	NC
12. Daptomycin	4–6 mg/kg/24 hr	4-6 mg/kg/24 hr	4-6 mg/kg/48 hr	NC	NC	NC
13. Linezolid	0.6 g/12 hr	NC	NC	0.6 g	NC	NC
14. Tigecycline	NC	NC	NC	No	No	100 mg × 1 dose 25 mg/12 hr
15.Metronidazole	1 g/24 hr	NC	NC	1 g	1 g	NC
16. Colistin	1–1.5 MIU/12 hr	1–1.5 MIU/24 hr	1–1.5 MIU/36 hr	No	No	NC
17. Isoniazid	5 mg/kg	NC	NC	300 mg	300 mg	Reduced dose
18. Ethambutol	15 mg/kg	NC	Stop drug	NC	NC	NC
19. Rifampicin	600 mg	NC	NC	No	-	Reduce dose
20. Fluconazole	400 mg LD + 200 mg/24 hr	100 mg/24 hr	10 mg/24 hr	200 mg	200 mg	NC
21. Voriconazole	6 mg/kg 12 hourly LD, 4 mg/kg 12 hourly	No IV, use PO	No IV, use PO	Usual dose IV/PO		6 mg/kg 12 hourly, 2 mg/kg 12 hourly
22. Amphotericin B	24 hr	3 days	5 days	No	No	NC

* Therapeutic drug monitoring recommended (TDM)
Abbreviations: MIU, million International units; NC, no change; PO, per os.

information on important interactions involving antimicrobial drugs used frequently in very ill patients in the ICU.

ADJUSTING DOSAGE SCHEDULES

Patients with hepatic or renal dysfunction often need modifications of drug dosage. Table 4 gives details regarding the use of antimicrobials against a background of renal or hepatic insufficiency in ICU patients.

Monitoring drug levels is particularly important in critically ill patients. Failure to attain therapeutic levels can have disastrous consequences, just as toxic levels add to the problems of a very ill patient. Monitoring drug levels, so as to avoid toxicity, is specially necessary in a patient population in whom the pharmacokinetics of a drug is difficult to predict. This is particularly so in patients whose hepatic or renal function is suspect, or in those who have clear evidence of hepatic or renal dysfunction. Unfortunately, in our set-up, monitoring drug levels is difficult, and till recently was non-existent. Fortunately, laboratories have now started to estimate serum levels of important drugs used in the ICU. This is of great help in adjusting the appropriate dose of these drugs (including antimicrobials), in very ill ICU patients.

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CHAPTER 47

Invasive Fungal Infections in the ICU

INTRODUCTION

Fungal infections occur not only in immunocompromised patients (see Chapter The Immunocompromised Patients), but also in patients who are under critical care for various problems, e.g. acute infections, trauma or major surgery, and who have a normal immune defense mechanism to start with. Perhaps the most important cause of fungal overgrowth and any systemic or deep-seated fungal infection in these patients is the prolonged use of broad-spectrum antibiotics which alter the bacterial flora, and promote the growth of unusual resistant organisms and fungi. Acute or critical illnesses in the course of time also temporarily depress the immune mechanisms within the body to some extent. Thus patients with unresolved or persistent septic infections, or long-standing untreated foci of infection, e.g. undrained abscesses, show a decreased capacity to respond to immunological challenges. All major surgical procedures are also followed by a depressed immunological response; this is related to an increase in suppressor cells, a fall in T4 lymphocytes, and alterations in lymphokine production. These changes are however temporary, and are quickly reversed as recovery progresses. In the presence of complications, the postoperative changes noted above are protracted, and may well play a role in predisposing the patient to both bacterial and fungal infections. Finally, poor nutritional status further depresses the immune defense mechanisms. Thus a combination of various factors, varying in degree in each individual critically ill patient, form a background against which fungal infections can occasionally supervene. The environment too perhaps has some part to play, e.g. clear-cut nosocomial outbreaks of invasive aspergillosis have been described in critical care units, and these have been related to the marked increase in air-borne spores of *Aspergillus fumigatus* in these units.

The important invasive fungal infections encountered in a critical care setting are candidiasis and aspergillus infections. Occasionally, infections with the mucor species are observed, particularly in diabetics or other severely immunocompromised patients. Other fungal infections are being increasingly recognized in the West; in our country, however, we are as yet blissfully unaware of their possible occurrence.

CANDIDAL BLOODSTREAM INFECTIONS

Epidemiology

Candida represents the commonest form of invasive fungal disease[1] in most ICUs all over the world. It now accounts for 12% of all hospital-acquired bloodstream infections (BSIs). Though there was a major increase in candida BSI in the 1980s, the incidence of BSI has now stabilized or even declined in the West. The incidence of BSI with candida varies in different ICUs in our country. We have noted a definite increase in candidal BSI in our unit; perhaps this holds for many units in the large urban centers of India. An important epidemiological trend in many western centers is the shift in the distribution of candidal species responsible for BSI, *Candida albicans* being responsible for only half of all BSIs caused by yeast. Recent data from the Prospective Antifungal Therapy Alliance (PATH) database from 2004 to 2008 showed that the incidence of candidemia caused by the non-albicans candida species was higher (54.4%) than *C. albicans* (45.6%). The commonest non-albicans species that were isolated being *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei.*[2] In our unit *C. albicans* is no longer the main isolate in BSI; there is a slow but definite increase in isolates of *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. krusei* and also an occasional presence of other rare candida species. *C. tropicalis* now is the main bloodstream isolate

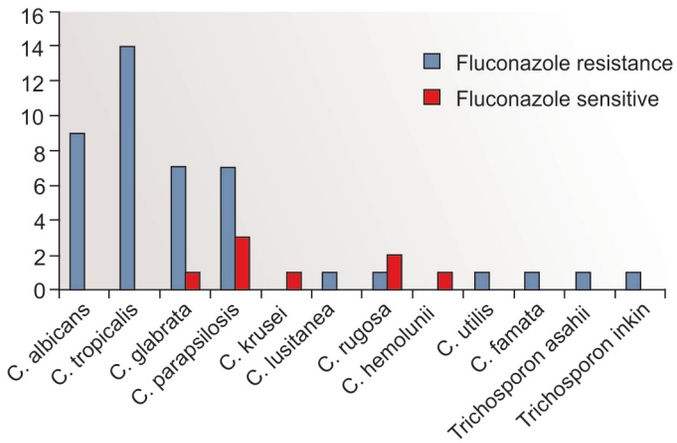

Fig. 1: Fluconazole resistance among yeast isolated from blood cultures (2010–2012)

constituting 14% of all bloodstream yeast isolates. It is possible that the increasing incidence of non-*C. albicans* species may be related to the extensive use of fluconazole not only as treatment but also as a prophylactic drug in patients in whom fungal infections are likely to occur. This epidemiological shift which is obvious in the West, but slowly making itself felt in our country as well, has important implications for therapy, because of intrinsic resistance of *C. glabrata* and *C. krusei* to fluconazole. Figure 1 illustrates the distribution of yeasts isolated from blood cultures and resistance to fluconazole.

A study on bloodstream fungal infection from the Sir Ganga Ram Hospital, New Delhi, India,[3] has also shown a significant increase in both candidemia and total antifungal use. There was increase in infections due to the non-albicans species and this was correlated to increasing use of fluconazole. The study also revealed the emergence and isolation of a novel species *C. haemolunii* with decreased susceptibility to both amphotericin B and azoles. The authors of this study have commented that decreased susceptibility to fluconazole, as well as the threat of emergence of cross-resistance to voriconazole against the background of high azole consumption, may limit the use of these agents as presumptive therapy for candida BSIs.

A study by Chakrabarti A et al (presented as a poster at the ID Week San Diego, 2012) included 25 ICUs across India and found that the incidence of candidemia was 7.0/1,000 ICU admissions over a 6-month period. This study highlighted the distribution of candidia species in these patients, the most common being *C. tropicalis* and the emergence of uncommon species like *C. haemulonii* and *C. rugosa*, *C. guilliermondii*, *C. pelliculosa* and also of azole resistant C. albicans and C. tropicalis. Figure 2 shows the distribution of various candida species in this study.

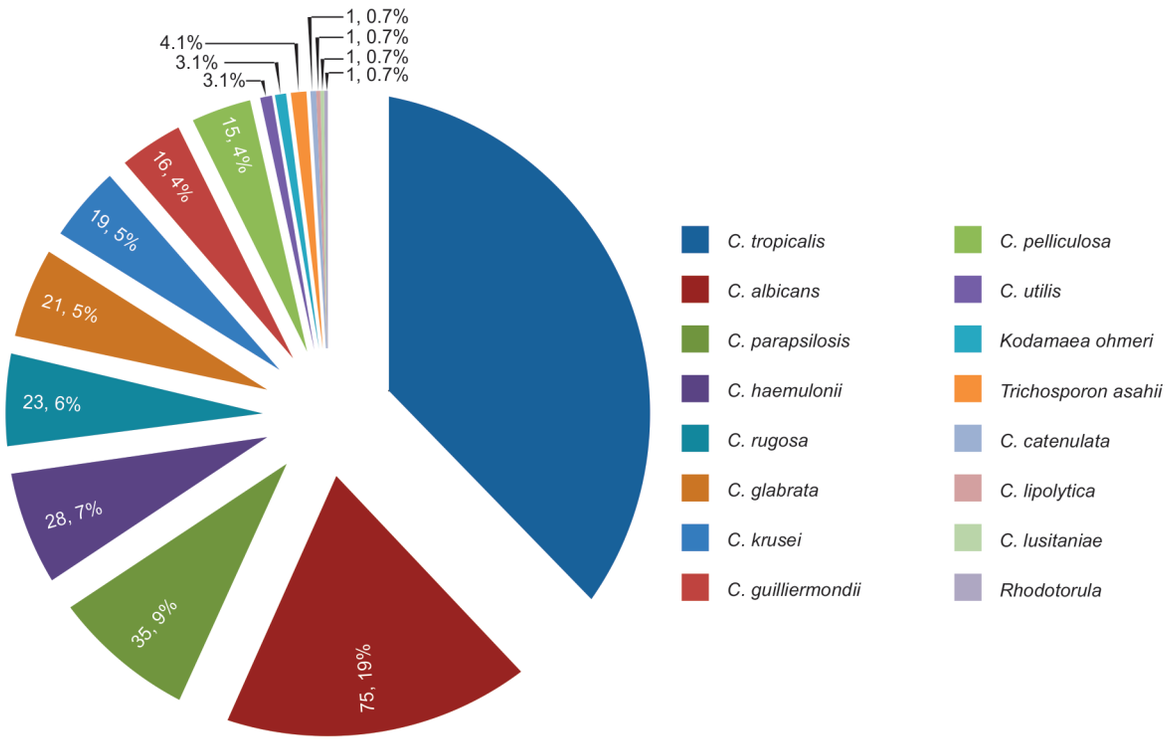

Fig 2 : Distribution of various candida species in candidemia patients

Source: Chakrabarti A et al. Candidemia in Intensive Care Units of India: a Six Months Interim Report on Active Surveillance. ID week 2012, San Diego. Poster Abstract Session: Clinical Mycology and Fungal Virulence October 18, 2012.

Box 1: Risk factors for invasive candidiasis

- Prolonged use of antibiotics
- Corticosteroids, immunosuppressive therapy
- Central venous catheterization
- Prolonged ICU stay
- Surgery
- TPN
- Diabetes, malignancy
- Organ transplant
- Dialysis
- Pancreatitis
- Multifocal colonization

Risk Factors for Invasive Candidiasis

Specific to the ICU, several risk stratification schemes exist to identify patients at high risk for candidemia. A multicenter cohort study from Spain[4] involving 1,699 adult ICU patients identified surgery, multifocal colonization, TPN and severe sepsis to be strong predictors of candidal infection. Another large cohort study from American and Brazilian ICUs identified the following features to predict invasive candidiasis. These factors were antibiotics, central venous catheter (CVC), TPN, dialysis, major surgery, pancreatitis, use of steroids and other immunosuppressive agents.[5]

Both these studies in our opinion have omitted one major risk factor for invasive candidiasis—*duration of ICU* stay. The longer the stay in the ICU, the greater the chance of the patient developing a fungal infection. What combination of risk factors stated above are more likely to cause invasive candidiasis is undetermined. The risk factors for invasive candidiasis are listed in Box 1.

According to the Indian study by Chakrabarti et al. quoted earlier, central venous catheterization, urethral catheterization and mechanical ventilation were seen as significant risk factors associated with candidemia in the ICU. Table 1 shows the various risk factors linked with candidemia as found in this study.

Proof of invasive candidiasis rests in a positive blood culture for candida. Unfortunately blood cultures are positive only in 50–70% of patients with invasive candidiasis. It is important to note that a positive blood culture for candida should never be ignored as a possible contaminant and should prompt search for the source of infection. Biopsy of specific lesions from a normally sterile site (e.g. lung, liver) demonstrating the histopathology of invasive candidiasis can give a definite diagnosis, but this is often not feasible in critically ill patients. Because of these difficulties in diagnosis, a non-culture based diagnosis test has been researched upon and recently approved by the Food and Drug Administration. This test is the 1-3-β-D-glucan test. 1-3-β-D-glucan is an important major component of the fungal cell wall and it can be detected from the blood and assayed in patients with invasive candidiasis. It has a sensitivity of 75–100% and a specificity of 88–100%. However, this is a broad spectrum assay that detects not just candida but also *Aspergillus*, *Fusarium*, *Acremonium*, *Saccharomyces* species.[6] The test therefore requires careful interpretation. In fact none of the currently available tests allow of a reliable diagnosis. Hence, in a febrile critically ill patient who is unresponsive to antibiotics and who has risk factors for invasive candidiasis, empiric treatment against candidal infection is justified.

Table 1: Risk factors associated with candidemia in the ICU

Risk factors	*No. of cases*
CVL catheterization	218
Urethral catheterization	201
Invasive mechanical ventilation	169
Drainage catheter	88
Antibiotic therapy	63
Dialysis	55
Total parenteral nutrition	55
Steroid therapy	61

Source: Chakrabarti A et al. Candidemia in Intensive Care Units of India: a Six Months Interim Report on Active Surveillance. ID week 2012, San Diego. Poster Abstract Session: Clinical Mycology and Fungal Virulence October 18, 2012.

Clinical Features

Pyrexia of unknown origin not responding to antibiotics therapy is the key presentation in most cases. Candidal infection can involve any organ system in invasive candidiasis. Liver and spleen involvement lead to hepatosplenomegaly. The kidney, lungs, brain may also be involved. Endophthalmitis is a rare but noteworthy feature in some patients.

Treatment[7]

Treatment should not await a confirmed culture. High risk cases presenting with fever and showing a sharp clinical deterioration should be promptly started on antifungal therapy. The CVC should as far as possible be removed. If absolutely necessary a new central line on the opposite side should be inserted.

For non-neutropenic hemodynamically stable patients, fluconazole is the drug of choice unless there is a suspicion of a fluconazole resistant species—e.g. history of a recent azole exposure or a history of previous colonization by *C. glabrata*, *C. krusei*. If used empirically the drug is given IV in a dose of 800 mg/day, the dose being adjusted with reference to renal function. The drug is continued till the offending candida species has been identified.

In neutropenic patients, or in hemodynamically unstable patients, or in ICUs where there is significant infection rate with fluconazole resistant species, an echinocandin is the drug of choice till species identification of the fungal isolate is made. The echinocandin generally used is caspofungin. Two other commercially available echinocandins are also available. These are micafungin and anidulafungin. Experience with

the last two echinocandins is however limited. Lyophylized amphotericin can also be used if there is intolerance to or unavailability of an echinocandins. Voriconazole is an acceptable alternative but offers no advantage over fluconazole. It is to be recommended as step-drown oral therapy for selected cases of candidiasis due to *C. krusei* or voriconazole susceptible *C. glabrata*. If infection has been caused by *C. parapsilosis*, fluconazole is preferred as these fungi are less susceptible to echinocandins.

The duration of therapy recommended is 14 days from the last positive cultures. If cultures remain negative treatment should continue for 7–10 days after the patient is afebrile. Treatment at times needs to be longer depending on the degree of infection and the site involved.

INVASIVE ASPERGILLOSIS

Invasive aspergillosis is less commonly encountered than invasive candidiasis. Sinopulmonary infection is most often observed, though many organ systems can be involved. *A. fumigatus*, *A. flavus* and *A. niger* account for nearly all human disease. Though the disease may rarely be encountered in immunocompetent individuals, it is most frequently seen in immunocompromised or immunosuppressant patients in the ICU.

The risk factors are—

- Prolonged neutropenia.
- Corticosteroids and immunosuppressive therapy.
- Solid organ transplant patients.
- Hemopoietic stem cell transplant patients.
- Advanced HIV with CD counts often below 200 cells/μL.
- Chronic granulomatous disease.

The clinical features have been discussed in the Chapter The Immunocompromised Patients.

Demonstration of the aspergillus in biopsy samples is the gold standard for diagnosis. A positive aspergillus culture from the blood though uncommon is also confirmatory. A bronchoalveolar lavage (BAL) culture positive for aspergillus should lend strong suspicion for invasive pulmonary aspergillosis, if clinical features are compatible with the diagnosis.

Computed tomography (CT) findings of the chest may suggest the diagnosis—cavitations, nodules, wedge shaped pleural based shadows suggesting pulmonary infarcts, the halo sign, the crescent sign may be observed. The clinical and imaging features as also the value of the galactomannan test and the β glucan test have been commented upon in the Chapter The Immunocompromised Patients.

Treatment[8]

According to a multicenter randomized open label trial comparing amphotericin B to voriconazole as initial therapy for invasive aspergillosis, voriconazole was associated with increased survival (76% vs 58%). Voriconazole is therefore generally recommended as first line therapy. Before voriconazole, itraconazole was used intravenously against invasive aspergillosis with reasonable success. Voriconazole has now replaced itraconazole in treatment. Posaconazole is an additional extended triazole for treating refractory disease.

The echinocandins (caspofungin) can be used as alternative therapy to voriconazole particularly in patients who cannot tolerate voriconazole or who are refractory to standard therapy. Many units use a combination of amphotericin B or amphotericin B lipid formulation and voriconazole in the treatment of severe invasive aspergillosis. There is however very little evidence for the increased efficacy and safety of this combination therapy.

The final drugs recommended as salvage therapy for invasive aspergillosis are micafungin and anidulafungin, two new echinocandins.[8] The experience with micafungin or anidulafungin is limited. The drugs are best kept in reserve for salvage therapy.

MUCORMYCOSIS

Mucormycosis is a life threatening mould infection caused by fungi belonging to the older Mucorales. The organisms causing this mould infection include Rhizopus, Rhizomucor, Absidia and Mucor. These organisms almost always have a predilection for immunocompromised patients and present with a rapid onset angioinvasive disease. Risk factors include diabetes, acidosis, solid organ and bone marrow transplant recipients, use of immunosuppressant drugs, iron overload, deferoxamine treatment.

Diabetes and in particular diabetic acidosis are major risk factors. Patients present with rhinocerebral disease that causes destruction of the nasal septum and paranasal sinuses; the disease then extends into and destroys the orbit and penetrates upward into the brain.

Pulmonary mucormycosis is the typical presentation in post-transplant patients. Invasion of vessels with ischemic necrosis of the tissue is a typical feature of this fungal disease.

Treatment[9] is with high dose amphotericin B 1–1.5 mg/kg per day or amphotericin B lipid preparation in doses of 5–7.5 mg/kg per day. Azoles and echinocandins are ineffective in mucormycosis.

Urgent surgical treatment is always necessary to excise and debride involved tissue in rhinocerebral disease. Surgery may also be necessary in pulmonary mucormycosis.

Early diagnosis is critical for survival. Diagnosis is made on clinical grounds and the presence of the fungus in scrapings of involved tissue, and of the fungus in the discharge from infected tissue. Delay in initiating treatment increases mortality. Posaconazole has been recently used as prophylaxis in severely immunocompromised patients. This drug has also occasionally been used as salvage therapy but is not a standard treatment for the disease.

The efficacies of antifungal agents are listed in Table 2. Doses and dosing adjustment of commonly used antifungal agents are listed in Table 3.

This is followed by a brief description on the role of amphotericin B in fungal infections.

Table 2: Efficacy of antifungal agents in fungal infections

	Amphotericin B or Amphotericin B lipid formulation	*Fluconazole*	*Voriconazole*	*Echinocandin*
C. Albicans	+	+	+	+
C. Tropicales	+	+	+	+
C. Glabrata	+	-	-	+
C. Krusei	+	-	+	+
C. Parapsilosis	+	+	+	+/-
Aspergillus	+	-	+	+
Cryptococcus	+	+	+	-
Mucorales	+	-	-	-
Fusarium	-	-	+	+/-

Note: Aspergillus terreus is intrinsically resistant to amphotericin B. *Aspergillus lentulus* is intrinsically resistant to azoles.

Table 3: Doses of commonly used antifungal agents

Drug	*Dose*	*Dose adjustment*
Invasive Candidiasis		
Amphotericin B	0.6–1 mg/kg/day, IV	None, careful monitoring of renal and liver function
Amphotericin B lipid formulation	3–5 mg/kg/day, IV	None, careful monitoring of renal and liver function
Fluconazole	400–800 mg/day, IV or PO	Renal insufficiency
Voriconazole	IV, 6 mg/kg every 12 hr for 2 doses followed by 3–4 mg/kg every 12 hour PO, <40 kg –100 mg every 12 hr; >40 kg –200 mg every 12 hour	Hepatic dysfunction
Echinocandins		
Caspofungin	70 mg loading dose followed by 50 mg/day, IV	Hepatic dysfunction
Micafungin	100 mg/kg	
Anidulafungin	200 mg loading dose followed by 100 mg/day, IV	None
Invasive Aspergillus		
Amphotericin B	1–1.5 mg/kg/day, IV	As listed above
Amphotericin B lipid formulation	5 mg/kg/day, IV	As listed above
Voriconazole	As listed above	As listed above
Echinocandins	As listed above	As listed above
Itraconazole	IV, 200 mg every 12 hr for 4 doses followed by 200 mg/day PO, 200–400 mg/day	Multiple drug interaction, IV not recommended for CrCl <30 mL/min
Mucormycosis		
Amphotericin B	1–1.5 mg/kg/day, IV	As listed above
Amphotericin B lipid formulation	≥5 mg/kg/day, IV	As listed above

Abbreviations: PO, by mouth; IV, intravenous; CrCl, creatinine clearance.

Amphotericin B

For poor developing countries, the cheapest of all antifungal agents against invasive fungal infection is amphotericin B deoxycholate and it is therefore appropriate to add a few additional remarks on this drug. The drug has important side effects and in critically ill patients it is best to start with a test dose of 1 mg in adults (0.5 mg in children <30 kg) given over 1 hour. This is followed after 4 hours by a dose of 0.5 mg/kg administered over 3–4 hours. Even if the test dose produces a reaction, 10 mg is administered after 4 hours. The dose is

increased by 15–20 mg daily so that the dose of 0.5–1 mg/kg is reached within 3–7 days. The drug is then continued daily till a total dose of at least 1–1.5 g is administered. In granulocytopenic patients empirically given amphotericin B should be continued till recovery from granulocytopenia ensues. Deep visceral infections may require a total dose of 2–3 g or even more.

Amphotericin B should be given in a 5% dextrose solution. Electrolyte solutions should be avoided, as they cause precipitation of the amphotericin B suspension. Side effects are common; pyrexia with chills is the most frequent side effect observed. Intravenous hydrocortisone in a dose of 50 mg given at the time of infusion often controls a severe pyrexial reaction. Other important side effects include hypotension, nausea, thrombophlebitis, hypokalemia and renal dysfunction with a rise in the serum creatinine level. A significant rise in the latter warrants a temporary stoppage of the drug; it is restarted when the creatinine level drops. Permanent renal tubular damage may occur when large doses (3–4 g) of amphotericin B are used.

Amphotericin B does not achieve significant concentration in the urine, CSF or peritoneal fluid. In cases of fungal meningitis, intrathecal administration of amphotericin B may be combined with intravenous therapy. The intrathecal dose is 0.5–1 mg dissolved in the CSF. The total dose should not exceed 15 mg. Arachnoiditis and motor or sensory disturbances may occur as complications. An Omaha reservoir is sometimes used for instillation of amphotericin B into the cerebral ventricles in patients with CNS fungal infection. The danger of introducing secondary bacterial infection is ever present with this mode of administration.

Clinical Resistance to Amphotericin B

Clinical resistance to amphotericin B is observed in severely immunocompromised patients, in patients with infected prosthetic valves or other foreign bodies, and in advanced visceral fungal infections involving the liver, spleen or kidneys.

Hepatosplenic candidiasis is a clinically resistant infection which may prove resistant to even high doses of amphotericin B. The development of fever, abdominal pain, or liver cell dysfunction occurring in a patient recovering from granulocytopenia should raise suspicion of candidal infection within the abdomen. Investigations should include ultrasound, CT and, if necessary, MRI imaging of the abdominal organs. A combination of amphotericin B and flucytosine or fluconazole should be promptly started. Therapy may need to be continued for several months, and may yet be unsuccessful.

Microbiological resistance to amphotericin B has been reported in *C. albicans*, *C. tropicales*, other candida species, as also against other fungi—*Trichosporon beigeli*, Fusarium species, and *Pseudallescheria boydii* species.[10] In the West, *Trichosporon beigelii*, Fusarium species, and *P. boydii* species are increasingly recognized causes of systemic fungal infections.[10] A combination therapy of high doses of amphotericin B with flucytosine or fluconazole is recommended as initial treatment. If unsuccessful, fluconazole plus flucytosine is advised for systemic fungal infections due to polyene resistant fungi.[10]

Systemic fungal infections originating from an infected foreign body, viz. an infected prosthetic valve, can never be controlled unless the foreign body is first removed. Fungal valvular endocarditis invariably necessitates removal of the valve. Further examples where removal of infected foreign bodies is mandatory include—

- Removal of central venous lines.
- Removal of infected ventriculoperitoneal shunts in patients with fungal infections of the CNS.
- Removal of urinary catheters in patients with candidiasis involving the urinary tract.
- Removal of a dialysis catheter in fungal peritonitis associated with peritoneal dialysis.

It is not enough to use antifungal drugs in the treatment of systemic fungal infections in critically ill patients. As always, overall critical care is of vital importance. An assiduous search to determine why systemic fungal infection occurred, and whether the source of infection can be controlled or eradicated is of great importance.

Flucytosine

Flucytosine is an antifungal drug that has not been discussed earlier. It is effective both orally and on intravenous use and is active against candida species and cryptcoccus. It enters cerebrospinal fluid as also urine and peritoneal fluid and is particularly useful in fungal (especially cryptococcal) infections involving the meninges and/or the neuroaxis. Its excretion is reduced in renal failure; the daily dose should therefore be adjusted in these patients. Its main disadvantage is the development of either primary or secondary drug resistance to a significant number of fungal isolates. There is also the danger of bone marrow suppression, particularly with use of toxic doses. The dose of flucytosine is 100 mg/kg of bodyweight orally, divided in four equal doses every 6 hours. The dose for intravenous infusions is 50 mg/kg infused over 20–40 minutes every 6 hours. If possible blood levels of the drug should be estimated and not allowed to go beyond 100–120 µg/dL.

As has already been mentioned, combination therapy with amphotericin B and flucytosine is often used in relatively resistant fungal infection. The drugs when used together are synergistic, so that the dose of amphotericin may be reduced in patients who do not tolerate its full dose. In cryptococcal meningitis, a combination therapy of 0.3–0.6 mg/kg of amphotericin B and the usual dose of flucytosine is more effective in sterilizing the CSF and prevents relapse. Alternatively, IV amphotericin B (0.7 mg/kg per day) can be used for the first 2 weeks, followed by fluconazole or flucytosine orally.

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SECTION

14

Surgical Infections in the Intensive Care Unit

- Postoperative Wound Infections
- Necrotizing Soft Tissue Infections
- Intra-Abdominal Sepsis
- Abdominal Compartment Syndrome

CHAPTER 48

Postoperative Wound Infections

INTRODUCTION

Surgical infections in the intensive care unit fall into the following two groups.

Infections Which Require Prompt Surgery

These include serious soft tissue infections like necrotizing fasciitis, acute inflammatory intra-abdominal disease, acute suppurative disease tucked away (and therefore not easily evident) in other parts of the human anatomy, e.g. the thorax, within the head and neck, or in the skeleton.

Acute inflammatory or acute suppurative disease within the abdomen accounts for most infections requiring definitive surgery. Important surgical problems within the abdomen include acute suppurative appendicitis, empyema of the gall-bladder, pancreatic suppuration, and peritonitis following a leak from the bowel. Peritonitis may be generalized or may be localized, and may ultimately result in an intra-abdominal abscess. A localized intra-abdominal abscess may go unrecognized, and is responsible for a hidden, or rather undiscovered source of systemic sepsis, septic shock and multiple organ failure. Pelvic suppuration is also an important and at times unrecognized source of systemic sepsis. Pelvic suppuration may present as pelvic peritonitis, pelvic abscess or suppuration involving the organs within the pelvis—chiefly tubo-ovarian suppuration.

Wound Infections Which Occur as a Complication of Surgery

Infected post-surgical wounds pose serious problems for critically ill patients in the ICU.[1] Major surgery performed for problems totally unrelated to infection can thus be complicated by wound infection. The rather hostile microbiological environment in the ICU, almost certainly encourages such wound infections. Besides nosocomial wound infections, the postoperative surgical patient is also exposed to other nosocomial infections prevalent in the ICU. These chiefly include nosocomial pneumonias, urinary infections and catheter (central line) related sepsis. These nosocomial complications can drastically influence the morbidity and mortality of surgical patients in the ICU, and call for prompt diagnosis and treatment.

POSTOPERATIVE WOUND INFECTIONS[1-4]

General Considerations

Wound infections account for about a quarter to a sixth of all nosocomial infections. Despite the most meticulous attention to surgical technique, a surgical incision exposes sterile tissue to some degree of contamination.[2] The rate of infection of a surgical wound mainly depends on the nature of the wound. Operative wounds are classified as (i) clean; (ii) clean-contaminated; (iii) contaminated; (iv) dirty and infected, based on the degree of contamination at the time of surgery. The incidence of postoperative wound infections in clean wounds may be less than 2%. On the other hand, in dirty and infected wounds, the incidence may be as high as 40%.[3] Table 1 gives the classification of surgical wounds and the incidence of wound infection.[3]

The propensity to infection in surgical wounds depends on a number of other factors—

- The degree of attention paid to preoperative, intraoperative and postoperative asepsis; ensuring adequate tissue perfusion and eliminating tissue dead space, reduces the incidence of postoperative infections.

Table 1: Classification of surgical wounds and incidence of wound infection

Type of wound	*Characteristics*	*Incidence of infection (%)*
Clean	Non-traumatic, inflammation absent, respiratory, genitourinary or GI tracts not breached	<2
Clean contaminated	GI, respiratory, biliary or genitourinary tracts entered without significant spillage	2–8
Contaminated	Gross spillage from GI tract	8–15
Dirty and infected	Acute bacterial inflammation present, traumatic wound with devitalized tissue, foreign body, fecal contamination, or delayed treatment	12–40

Source: Adopted from Cruse PJ. Wound infections: epidemiology and clinical characteristics. In: Howard RJ, Simmons RL (Eds). Surgical Infectious Disease. New York: McGraw Hill Companies; 1988. p. 320.

- The stage of disease when surgery is performed. Surgery performed late in the natural history of a disease is often prolonged, complicated and more likely to result in postoperative infections.
- The duration of preoperative hospitalization influences the incidence of wound infections. The infection rate almost doubles with each week of hospitalization prior to surgery. Colonization with nosocomial and often resistant bacteria is common, particularly if the patient has been in the ICU prior to surgery.
- The risk of wound infection increases with prolonged surgery, the liberal use of cautery, and the placement of drains.
- A concurrent but remote infection (e.g. pulmonary infection, urinary tract infection or skin infection) increases the likelihood of wound infection. It is always wise to postpone elective surgery till such infections are eradicated.
- Infections are more likely in the old, feeble, diabetic, malnourished, anemic patients and those with chronic hepatitis or renal or cardiac dysfunction.
- Immunosuppression because of disease or drugs (antimitotic drugs, corticosteroids) is associated with a far greater risk of wound infection.
- A history of shock or prolonged hypotension during or soon after surgery is a risk factor—probably related to poor tissue perfusion.
- An important factor which decides the nature and severity of wound infection is the nature of organisms likely to contaminate the wound. Possible contamination with *Staphylococcus aureus*, Gram-negative organisms, or anaerobes, like clostridia, can give rise to violent tissue infections in spite of all the care in the world.[1]

Factors predisposing to postoperative wound infections are listed in Box 1.

Box 1: Predisposing factors for postoperative wound infections

- Poor preoperative, intraoperative or postoperative asepsis
- Prolonged or complicated surgery, or surgery performed late in the natural history of the disease
- Prolonged hypotension during or soon after surgery
- Prolonged period of hospitalization particularly in the ICU
- Presence of coexisting infection elsewhere in the body (lungs, skin, urinary tract)
- Adverse host factors, e.g. old, feeble, malnourished, anemic patients and those with hepatic or renal dysfunction
- Immunocompromised patients
- Pathogenicity of infecting organism

Clinical Features

The diagnosis of wound infection is based on a history, physical examination and the results of Gram stain and culture report of a discharge from the wound.[1-3,5,6] Wound pain due to infection may be difficult to distinguish from postoperative incisional discomfort. Most wound infections occur between the fourth to seventh day of surgery. Fever occurring 2–4 days after surgery should prompt examination of the wound, which may show erythema, edema, tenderness, warmth and often purulent discharge. Rarely a crepitus may be palpated. Deeper soft tissue infections may show no physical signs initially—particularly so in obese patients.

The microbiological spectrum responsible for wound infections is vast. Staphylococcal infections generally occur 4–6 days after surgery. The infection is well localized, painful and purulent.[6]

Gram-negative wound infections usually present with fewer local inflammatory signs, but with systemic features of fever, tachycardia and leucocytosis. Systemic sepsis may follow depending on the virulence of the organisms, and the resistance of the host. Gram-negative infections are usually due to contamination by enteric bacilli as well as by anaerobic streptococci and by *Bacteroides fragilis*. The incubation period for most of these infections is 7–14 days.[6] The potential gastrointestinal sources for such infections should be carefully looked for.

Fever, and severe pain in a surgical or traumatic wound accompanied by a progressively toxic state should lead to a suspicion of a wound infected by Group A streptococci or clostridia.[5] Early diagnosis, use of appropriate antibiotics and prompt surgical treatment are lifesaving.

Treatment

Surgical Drainage and Debridement

This should be left to the surgeon's expertise. The principle in management is drainage of infections and debridement of necrotic tissue. Drainage requires removal of skin sutures or staples, and laying the wound open. Dressings should be done daily or as often as instructed by the surgeon. The wound is

allowed to granulate and heal by secondary intention. If the wound is clean and clear of infection, secondary suturing may be done.

Antibiotics

Antibiotics are invariably used except for the very mild and superficial infections. The empiric choice of antibiotics in severe wound infections depends on the clinical picture and the nature of the surgery performed. Antibiotic therapy may be suitably modified after culture sensitivity reports of the discharge from an infected wound are available.

Hyperbaric Oxygen

The use of hyperbaric oxygen in certain infections will be commented upon in the section on Clostridial Myonecrosis in Chapter Necrotizing Soft Tissue Infections.

Antibiotic Prophylaxis[7,8]

Prophylactic antibiotics decrease the incidence of wound infections. The selection of the antibiotic depends on the possible pathogens in a given situation, and should be left to the discretion of the surgeon. The commonly used antibiotics for prophylaxis include either a third generation cephalosporin like ceftazidime 1 g intravenously, or a second generation cephalosporin like cefazolin 1 g intravenously, or an aminoglycoside like gentamicin 60–80 mg intravenously. It is important to stress that the unnecessary, indiscriminate and prolonged use of powerful antibiotics for prophylaxis can cause untoward side effects. These include hypersensitivity reactions, possible toxic effects (as on the kidneys with the use of aminoglycosides), and above all the emergence of drug-resistant superinfections. A single agent generally suffices for prophylactic therapy. This should be given immediately prior to the skin incision and should be repeated during surgery if this exceeds 3 hours, or twice the half-life of the drug. Most surgeons in the West do not continue antibiotics beyond the first day, as they believe that continuing the drug does not confer any additional benefit. In our country many surgeons prefer to continue the antibiotic for 5–7 days. In contaminated wounds or dirty and infected wounds, the extended use of antibiotics for a number of days after surgery, as best judged by the surgeon, is accepted practice.

In clean surgical wounds involving open heart surgery or intracranial surgery, the use of antibiotics for more days, is also justified. It is however doubtful if extended use in these patients confers any special benefit.

Mechanical cleansing of the bowel plus administration of a non-absorbable oral antibiotic is generally done to reduce the bacterial load in the colon and the distal small bowel before colorectal surgery. Oral amoxicillin is the antibiotic most often used. Metronidazole 400 mg thrice daily is also given for 4 days prior to surgery to reduce the load of anaerobic organisms within the large bowel. Most surgeons also use a systemic antibiotic for prophylactic purposes just before the skin incision. This combined approach of oral and systemic antibiotic prophylaxis reduces the bacterial flora within the gut, and helps to reduce the incidence of septic complications.

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CHAPTER 49

Necrotizing Soft Tissue Infections

INTRODUCTION

Necrotizing soft tissue infections (NSTIs) cover a wide range of infections in the soft tissue compartment. They spread very rapidly causing extensive necrosis and gangrene of the dermis, subcutaneous tissue, fascia and often extend into the underlying muscle (myonecrosis) and the tissue beneath the muscle. NSTIs include a spectrum of diseases which range from necrotizing fasciitis to Fournier's disease and gas gangrene. Though many different terms have been used to describe these infections, the term NSTI encompasses all necrotizing infections involving the soft tissue compartment. They have common clinical, pathophysiological, microbial, treatment and outcome characteristics.[1]

Necrotizing soft tissue infections are generally community-acquired. It can involve any part of the body but usually affects the upper and lower extremity and occasionally involves the groin and perineal areas. The infection can however occur after surgery, presenting as a wound infection even after minor surgical procedures.

RISK FACTORS

More than 80–90% of infections occur in patients who have pre-existing comorbidities.[2,3] The two perhaps most important risk factors are diabetes, present in 56–70% of cases[3] and the presence of a portal of entry. Portals of entry include surgery, needle punctures as after injections (particularly with contaminated needles used by drug addicts), minor abrasions and trauma. Blunt trauma or muscle strain with hematoma formation is also implicated as a risk factor. Other risk factors postulated are advanced age, peripheral vascular disease, chronic alcoholism, cirrhosis, chronic liver disease, cancer, use of immunosuppressant drugs and intravenous drug abuse.[2,3] Pre-existing comorbid states that contribute to mortality include cardiopulmonary disease, cancer and malnutrition.[4] Although pre-existing conditions increase both the risk for NSTI and mortality from NSTI, the main risk factor for mortality is the time to surgical debridement. The greater the time lag between the early symptoms of an NSTI and surgical debridement, the greater the risk of death (mortality 38%). The lesser the time lag, the better the outcome (mortality 4%).[4]

PATHOPHYSIOLOGY

The pathophysiology of all NSTIs is similar. Organisms gain entry through a break in the skin barrier causing a soft tissue infection in the dermis, superficial fascia of the subcutaneous tissue, initially sparing the overlying skin and underlying muscle. The rapidly spreading infection causes thrombosis of penetrating vessels with resulting necrosis of tissue supplied by these vessels. There is therefore a necrosis of dermis, fascia, subcutaneous tissue ultimately also involving the underlying muscle and overlying skin. Microorganisms multiply in this necrotic tissue. Systemic spread of infection can cause overwhelming severe sepsis with septic shock. Toxic shock syndrome results if the toxin is associated with infection by the group A *Streptococcus*. Muscle involvement generally occurs late, except with clostridial infection when muscle involvement can be early.

MICROBIOLOGY[5]

Though NSTIs can be caused by a single microbe (monomicrobial), more often than not the cause is polymicrobial. Organisms in polymicrobial infections include Gram-positive, Gram-negative organisms, anaerobes and aerobes. Polymicrobial infections are virulent and lead to a synergism between facultative aerobes and anaerobes. Monomicrobial infections occur in 15–30% of cases, the most common organism responsible for this infection being the group A *Streptococcus*. Necrotizing fasciitis is classically caused by *Streptococcus pyogenes* infection. Occasionally, monomicrobial infections are caused by *Clostridium* or *Staphylococcus aureus*. The most frequent Gram-negative organisms found in polymicrobial infection are *E. coli, Klebsiella*, *Pseudomonas*, *Enterobacter* and *Acinetobacter*. Though the management of all NSTIs is basically similar, identification of the infecting organism on culture may guide a more appropriate choice of antibiotics.

CLINICAL FEATURES[2,3,6,7]

The infection begins with fever and the appearance of a localized, red, indurated painful swelling at the site of minor trauma or at the site of a surgical wound. At times no evidence of even minor trauma is available both on history and physical examination. Pain is often a predominant feature and the significance of this is often ignored as the wound or infected area appears reasonably clean to start with. The infection spreads very rapidly with increasing pain, fever and toxemia. Characteristic local features include edema, violaceous discoloration, pain beyond the zone of the inflamed area, and the appearance of vesicles and hemorrhagic bullae. A palpable crepitus may be present and is a diagnostic feature. When the presence of crepitus is in doubt, an X-ray of the soft tissues, or better still a magnetic resonance imaging (MRI), may demonstrate gas in tissue planes. Within a few days extensive necrosis and sloughing of skin, subcutaneous tissue, fascia and at times even of the muscle occurs. Fever, tachycardia, tachypnea and overwhelming sepsis are often present. The mortality is as high as 30–70%; death being due to sepsis, septic shock and multiple organ failure.

DIAGNOSIS

The diagnosis is easy when there is clear evidence of tissue necrosis. Initially NSTIs are often misdiagnosed as cellulitis or abscess since both necrotizing and non-necrotizing soft tissue infections cause pain, erythema, induration and swelling. The presence of necrotic bullae immediately point to an NSTI; but this occurs late in the natural history. Points which should arouse suspicion of a possible NSTI are pain out of proportion to physical findings,[2] tenderness to palpation beyond the area of skin involvement, lack of a definite margin to the inflammation and a dusky erythema. The presence of bullae and/or crepitus on palpation though late in the evolution of the illness confirms the diagnosis.

INVESTIGATIONS

Blood culture in severe cases reveals bacteremia. There is marked leukocytosis. Severe anemia is due to both hemolysis and infection. Sepsis can lead to disseminated intravascular coagulopathy with a deranged coagulation profile. With extensive involvement of muscle (myonecrosis), rhabdomyolysis occurs and contributes to renal failure. Investigations assessing function of different organ systems are necessary.

When the clinical diagnosis is in doubt a fine needle aspiration or an incisional biopsy should be performed. These procedures may demonstrate the organisms on Gram stain. The material obtained should also be cultured on both aerobic and anaerobic media, and an antibiotic sensitivity of the organisms grown should be asked for.

Imaging Studies[8]

Soft tissue radiographs may demonstrate subcutaneous emphysema. An MRI study of the affected area picks up air in the soft tissues that can be missed by soft tissue radiography. This finding is not necessary for diagnosis and in any case may occur late in the disease.

MANAGEMENT

The principles of management are early diagnosis, prompt excision and debridement of all involved necrotic tissue, use of immediate empiric broad spectrum antibiotic therapy and critical care with support to all organ systems. Nutritional supplementation is invariably needed to meet the increased metabolic needs of the patients. In all patients, particularly in diabetics (who are at great risk for NSTIs), strict glycemic control should prevail.

Excision and Debridement

Necrotizing soft tissue infections (these include necrotizing fasciitis, Fournier's disease and gas gangrene) are life-threatening infections in which extensive surgical excision and debridement are necessary for survival. Delay in surgery significantly increases mortality. Debridement needs to be extensive, as infection is present well beyond the margins of the involved skin area. Incomplete debridement leads to further spread of necrosis. The margins of the excised area after surgery must appear perfectly healthy. The wound should be lightly packed and dressed; planned surgery may be required every 24–48 hours to ensure that ongoing necrosis is not present. Further excision and debridement is performed, if necessary. Repeated dressing change should be done in the

early days after debridement to ensure that the wound is clean and there is no evidence of recurrence or of ongoing infection. Wounds that cannot be closed by primary suture require split thickness skin graft.[3] The use of hyperbaric oxygen has been advocated following surgery. Its use in the management of NSTIs to reduce morbidity and mortality has however not been established. Hyperbaric oxygen therapy should be given a try following surgical excision and debridement in patients with clostridial myonecrosis.[9]

Antibiotic Therapy

Streptococcus pyogenes infection causing necrotizing fasciitis responds best to penicillin G, two mega units intravenously every 4 hours. Clindamycin is a suitable alternative. However, since necrotizing fasciitis can be caused by other organisms and since infection is much more often polymicrobial than monomicrobial, prompt broad spectrum antibiotic therapy should be started the moment a diagnosis is made or strongly suspected. Antibiotics should cover Gram-positive, Gram-negative organisms and anaerobes. Gram-positive coverage should be given by using penicillin or an extended spectrum penicillin derivative (like piperacillin tazobactum) or by vancomycin in penicillin allergic patients. Gram-negative coverage should be given with either a third generation cephalosporin or carbapenem and anaerobic cover with clindamycin or metronidazole.[9] Clindamycin has been particularly useful in children as it blocks exotoxin and M protein production leading to decreased inflammation and sepsis.[10] If a staphylococcal infection is suspected vancomycin 500 mg 6 hours or 1 g twice daily should be added to the antibiotic regime.

Antibiotics should be continued till the debridged wound is clean and infection has been controlled.

Critical Care

Critical care is vital for survival. These patients require fluid and electrolyte replacement as also cardiovascular and renal support. Ventilator support is often necessary. Critical care is as for severe sepsis and septic shock.

Nutritional Support

As mentioned earlier nutritional supplementation is important for overall care.

CLOSTRIDIAL MYONECROSIS[5,7,9]

Clostridial myonecrosis requires special mention for two reasons—

1. Infection by clostridia often produces early muscle necrosis.
2. This fulminant infection though rare is still encountered in poor developing countries.

Clostridial myonecrosis is a quick spreading fulminant infection, also known as gas gangrene; it is fortunately rare. It follows gross contamination of traumatic wounds by manure and is more likely to occur in the presence of devitalized tissue and poor perfusion. It can also occur when surgery is performed in a nonsterile environment where there is little regard for asepsis. In poor developing countries, there are operation theaters in smaller towns where conditions for surgery leave a lot to be desired. Clostridial myonecrosis in our country is a rare but important cause of wound infection in septic abortions. Operations on the gallbladder or large bowel can also rarely produce clostridial infection. The wound in clostridial myonecrosis is pale, painful with a watery, serous, or a serosanguinous discharge; above all it has a putrid smell. Crepitus is frequent; however, it may be absent in the early stages of infection. It is to be noted that crepitus in a wound infection can be produced by gas-forming organisms other than clostridia. Clostridial infection spreads rapidly and can lead to gangrene, overwhelming sepsis, shock and death. A Gram stain of the discharge from the wound shows Gram-positive cocci and a few neutrophils. A quick diagnosis, the use of appropriate antibiotics, and rapid surgical excision and debridement are necessary as in necrotizing fasciitis.

Investigations

The white blood cells (WBC) count is usually raised with an increase in the mature and immature neutrophils. Gram stain and culture from the wound discharge help to identify the pathogens causing the wound infection. A sensitivity test to various drugs helps in the choice of an appropriate antibiotic. Most experienced surgeons can predict with a fair degree of accuracy, the nature of the infection from the history, the surgery performed and the appearance of the wound.

Management

Crystalline penicillin alone in massive doses of 2–4 million units intravenously 4 hourly can control clostridial myonecrosis and monomicrobial cellulitis. Critical care of the patient involves cardiorespiratory support and attention to the functions of other organ systems as outlined in the Chapter Sepsis and Septic Shock. Critical care is vital for survival.

Use of Hyperbaric Oxygen[10]

Hyperbaric oxygen as a mode of treatment has been recommended as an adjunct to surgery and to antibiotic therapy for clostridial myonecrosis and for other soft tissue necrotizing infections. Hyperbaric oxygen is bactericidal for *Clostridium perfringens* and bacteriostatic for other anaerobic bacteria. Hyperbaric oxygen has however no effect on the toxin already produced; it can only reduce further production of exotoxin. It leads to an arrest of further necrosis, and often produces a visible improvement in the wound. As many as 14–15 sessions in the hyperbaric chamber may be necessary. The difficulty often lies in transporting very ill patients to a distant center.

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CHAPTER 50

Intra-Abdominal Sepsis

GENERAL CONSIDERATIONS

One of the most important surgical problems requiring intensive care is intra-abdominal sepsis. Intra-abdominal infections (IAIs) are currently classified into uncomplicated or complicated. In uncomplicated IAIs, the infection involves a single organ and does not involve the peritoneum. In complicated IAIs, the infection spreads beyond the organ causing either a localized peritonitis (an intra-abdominal abscess) or a generalized peritonitis. The merit of this classification is dubious as what appears clinically as uncomplicated, not uncommonly is termed complicated at surgery.

Intra-abdominal infections can also be classified into community acquired or nosocomial. Nosocomial infections carry an increased mortality as these patients are more seriously ill, and have an increased propensity to infections caused by multi-drug resistant organisms. The classification of IAIs should also take into consideration the clinical severity—i.e. whether the patient has merely sepsis, severe sepsis or septic shock. Patients with septic shock have the highest mortality.

The most frequent site of intra-abdominal sepsis is the peritoneal cavity. If generalized, it results in generalized peritonitis; if localized, it forms an intraperitoneal abscess. Perhaps the commonest site of an intraperitoneal abscess is in the right lower quadrant in association with acute appendicitis or a perforated duodenal ulcer. Localized intraperitoneal abscesses also occur in the left lower quadrant, and the pelvic, subhepatic and subphrenic spaces. Less frequently they may be found in the lesser sac or between the loops of the intestine.

Retroperitoneal abscesses occur in the space between the transversalis fascia and the retroperitoneum. They may occur posteriorly or anteriorly. Posterior retroperitoneal abscesses are usually related to suppuration within the kidneys, pancreas or the spine. Rarely they can be due to an infected blood clot. Anterior retroperitoneal abscesses occur following surgery performed for an intra-abdominal infection.

Visceral abscesses occur most often within the liver and the pancreas. An empyema of the gallbladder is also best considered an abscess. A tubo-ovarian abscess is an important focus of suppuration within the pelvis. Occasionally, visceral abscesses can form in other organs like the kidney or the spleen.

The grave danger of any form of intra-abdominal suppuration is progressive sepsis leading to septic shock and to multiple organ failure. Critically ill patients who develop intra-abdominal sepsis fall into two groups. The first consists of patients with less severe infections and good immune responses, so that the infection is contained and an intra-abdominal abscess results. These patients are less likely to progress to multiple organ failure. The second group comprises of those whose defense mechanisms are either very poor or suppressed, or those whose defenses are overwhelmed by virulent pathogens. These patients often develop generalized peritonitis without the formation of a localized abscess, and progress rapidly to septic shock and multiple organ failure. Death often results in spite of good critical care, surgery, antibiotics and nutritional support.

ETIOLOGY[1]

The most common causes preceding intra-abdominal suppuration are perforated peptic ulcer, acute appendicitis and acute diverticulitis. Perforation of any portion of the gut within the abdominal cavity, whatever the etiology, leads to peritonitis and intra-abdominal sepsis. Besides a perforated peptic ulcer, other important perforations

include appendicular perforation, diverticular perforation, perforation of the small bowel in enteric fever and perforation of a tuberculous ulcer. Corticosteroids can cause a peptic ulcer which may perforate, and nonsteroidal anti-inflammatory drugs can induce perforation in any portion of the gastrointestinal tract, including the large bowel. Occasionally, perforation with localized or generalized peritonitis can occur in inflammatory bowel disease.

Gangrene of the bowel from strangulation and obstruction, or from mesenteric vascular ischemia or occlusion are important causes of peritonitis.

Rupture of an empyema of the gallbladder or a gangrenous cholecystitis also causes generalized peritonitis. Acute inflammatory disease within the pelvis initially causes pelvic peritonitis, which may progress to a generalized peritonitis. Acute salpingitis, tubo-ovarian abscess are the classic examples of inflammatory pelvic pathologies. Acalculous cholecystitis and acute pancreatitis can complicate the course of a critical illness and are believed to be related to poor perfusion states in critically ill patients. In our country, septic abortion and puerperal sepsis are important causes of peritonitis.

In a critical care setting, low perfusion states, as observed in cardiogenic shock, congestive heart failure or shock due to any cause, can cause ischemia to the gut with a breach in its anatomic integrity.

Trauma to the abdomen either blunt or penetrating is also an important cause of intra-abdominal sepsis.

Postoperative peritonitis may be the direct result of abdominal surgery. It is more lethal than the other forms of peritonitis. Peritonitis following surgery is most commonly due to anastomotic dehiscence. Ischemia, infection, hemorrhage can all singly or in combination promote dehiscence. Excessive spillage and soiling of the peritoneum during handling of viscera during surgery can also lead to postoperative intra-abdominal sepsis. In gynecological operations on the pelvic viscera, an uncommon but important cause of postoperative peritonitis is an ileal perforation a few inches above the ileocecal junction. In my opinion, this is related to undue pressure on the ileocecal area exerted by a retractor during surgery. A small area of the ileum is devitalized or suffers pressure necrosis, and this perforates on the third or fourth postoperative day. Diagnosis may be difficult and delayed, leading to disastrous consequences.

Primary peritonitis is due to a generalized peritoneal infection unrelated to any intra-abdominal perforation or septic pathology. The most important background against which primary bacterial peritonitis occurs is in patients with cirrhosis of the liver with ascites. Infection is generally due to gram-negative organisms; it is probably hematogenous in origin. Primary bacterial peritonitis is also observed in patients with nephrotic syndrome, systemic lupus erythematosus and very rarely in immunocompromised individuals. A primary pneumococcal peritonitis is a dangerous entity in children, and is often mistaken for peritonitis following an appendicular perforation. Box 1 lists the common causes of intra-abdominal sepsis.

Box 1: Common causes of intra-abdominal sepsis

- Gastrointestinal—
  - Perforations—
    - Perforated gastric or duodenal ulcer
    - Perforation of hollow viscus or any part of the gut
    - Enteric or tuberculous ulcer
    - Inflammatory bowel disease
    - Diverticulitis
    - Iatrogenic [corticosteroid and nonsteroidal anti-inflammatory drugs (NSAID) use]
  - Infection—
    - Acute appendicitis
    - Diverticulitis
    - Gangrene from strangulation
    - Obstruction
    - Ischemia to the bowel
- Acute necrotizing pancreatitis
- Cholecystitis (acute, acalculous, gangrenous)
- Liver abscess (pyogenic, amebic), splenic abscess
- Pelvic pathologies—
  - Acute salpingitis
  - Tubo-ovarian abscess
  - Septic abortions/puerperal sepsis
- Perinephric/Retroperitoneal abscesses
- Trauma to the abdomen
- Following abdominal surgery
- Low-perfusion states (congestive cardiac failure, shock of any etiology)
- Primary bacterial peritonitis—
  - Cirrhosis of liver with ascites
  - Nephrotic syndrome
  - Systemic lupus erythematosus (SLE), other immunocompromised states
  - Pneumococcal peritonitis in children

PATHOPHYSIOLOGY[2]

The term peritonitis used without qualification, refers to acute bacterial suppurative peritonitis. Presence of sterile bile, blood or gastric acid in peritoneal cavity can also cause intense peritoneal irritation, and a chemical inflammation which is clinically indistinguishable from surgical peritonitis. The notable difference in these situations is the absence of bacterial infection, which when present plays a crucial role in the evolution of the natural history and the fatal outcome.

Bacterial contamination of the peritoneum is countered by local peritoneal defenses, and by a general immune response. The following pathophysiological changes are observed in suppurative peritonitis—

1. Local inflammation of the peritoneum.
2. Adynamic ileus.
3. Hypovolemia, chiefly related to (1) and (2) above.
4. Changes in other organ systems secondary to (1) and (2) above.
5. Hormonal and metabolic changes related chiefly to the immediate and acute stress of infection.
6. The evolution of the sepsis syndrome.

The sepsis syndrome is a systemic response of the body to bacteria, their toxins and to other bacterial products. Sepsis and the semantics of clinical states closely associated with sepsis have been discussed in the Chapter Sepsis and Septic Shock. It is worth stressing that intra-abdominal sepsis can be fulminant, and can quickly graduate to septic shock, multiple organ dysfunction and death. In earlier years, before intensive care came into being, most patients with generalized suppurative peritonitis died before sepsis with multiple organ system failure could fully evolve. Sepsis is due to endotoxins and other toxins of bacteria and their products, having far-reaching effects on all organ systems of the body. The syndrome however is not just the direct result of infection; it is also partly due to the unorchestrated response of the defense mechanisms of the body to infection. This is dealt with at length in the Chapters Sepsis and Septic Shock and Multiple Organ Dysfunction Syndrome. Localized undrained intra-abdominal abscesses (peritoneal, retroperitoneal or visceral) can also lead to the syndrome of sepsis and multiple organ failure. The tempo of the evolution of the syndrome with a localized abscess is generally slower than with generalized suppurative peritonitis.

The section below briefly deals with the pathophysiological changes listed under points (1) to (5). It then proceeds to mention the pathogenic factors which determine the severity of intra-abdominal sepsis.

Local Peritoneal Inflammation

The local response to a peritoneal insult is characterized by hyperemia of the peritoneum with vascular congestion, edema and transudation of fluid from the extracellular interstitial compartment into the abdominal cavity. This transudation is accompanied by the diapedesis of polymorphonuclear leukocytes. It is followed by exudation of a protein-rich exudate containing large quantities of fibrin and other plasma proteins. Clotting of this protein-rich exudate results in sticking together of the bowel loops to other viscera and the parietes in the areas of inflammation. This helps to localize the area of peritoneal contamination, to some extent.

Adynamic Ileus

Initially there is a short period of bowel hypermotility; motility is then depressed, and is followed by a complete adynamic ileus. The gut distends and is filled with fluid and air, most of the latter being swallowed air. Fluid secretion into the gut is markedly enhanced, whilst absorption of fluid from the gut is markedly impaired. There is therefore sequestration of a large volume of fluid within the lumen of the gut.

Hypovolemia

The loss and sequestration of fluid in the gut and in the peritoneal cavity may be marked and results in a fall in the volume of the interstitial tissue compartment and in the circulating volume within the vascular compartment. Fluid is also trapped as edema beneath the mesothelium of visceral peritoneal linings, adding thereby to the volume of water, electrolytes and proteins translocated into the third space. The degree of loss of extracellular fluid into this nonfunctional third space is proportional to the surface area of the peritoneum involved. The volume of sequestrated fluid may be as large as 4–6 liters in 24 hours.

Secondary Changes in Other Organ Systems

Cardiac Response

Cardiac response is conditioned by hypovolemia and progressive metabolic acidosis. Diminished venous return due to a fall in circulating volume leads to a fall in cardiac output, hypotension, a decrease in oxygen transport and to poor oxygenation of tissues. This promotes metabolic acidosis, which in turn further depresses cardiac function. The clinical importance of this should never be forgotten. Expanding the extracellular and intravascular compartments by intravenous infusions can reverse the above trends. In fact, if the patient is made normovolemic and survives the initial crisis, the circulatory state often graduates to that typically seen in sepsis. The hemodynamic changes are then characterized by a high cardiac output, hypotension and a low systemic peripheral vascular resistance (see Chapter Sepsis and Septic Shock). Even so, the tissue demand for oxygen is often inadequately met, so that tissue hypoxia results.

Renal Changes

These are secondary to hypovolemia, fall in cardiac output, and the effects of increased secretion of the antidiuretic hormone and aldosterone (see below). Renal perfusion suffers and there is a fall in the glomerular filtration rate due to the prerenal factors stated above. Renal insufficiency develops to a varying extent and enhances metabolic acidosis.

Respiratory Changes

Abdominal distension due to ileus, together with restriction of diaphragmatic and intercostal movements due to pain, results in a fall in the tidal volume. This predisposes to atelectasis, which in turn results in a ventilation-perfusion mismatch, and a fall in the PaO_2.

Hormonal and Metabolic Changes

Peritonitis causes an almost immediate response from the adrenal medulla. There is an outpouring of epinephrine and norepinephrine into the blood, resulting in vasoconstriction, tachycardia and sweating. There is also an increased secretion of adrenocortical hormones for the first 2–3 days following a peritoneal insult. Secretion of antidiuretic hormone and aldosterone is also increased, causing a reduction in urine output with conservation of sodium and water. Water retention may exceed sodium retention, leading to hyponatremia.

The metabolic rate is generally increased with a corresponding increase in oxygen demand by the tissues. For reasons stated above, the cardiopulmonary system is unable

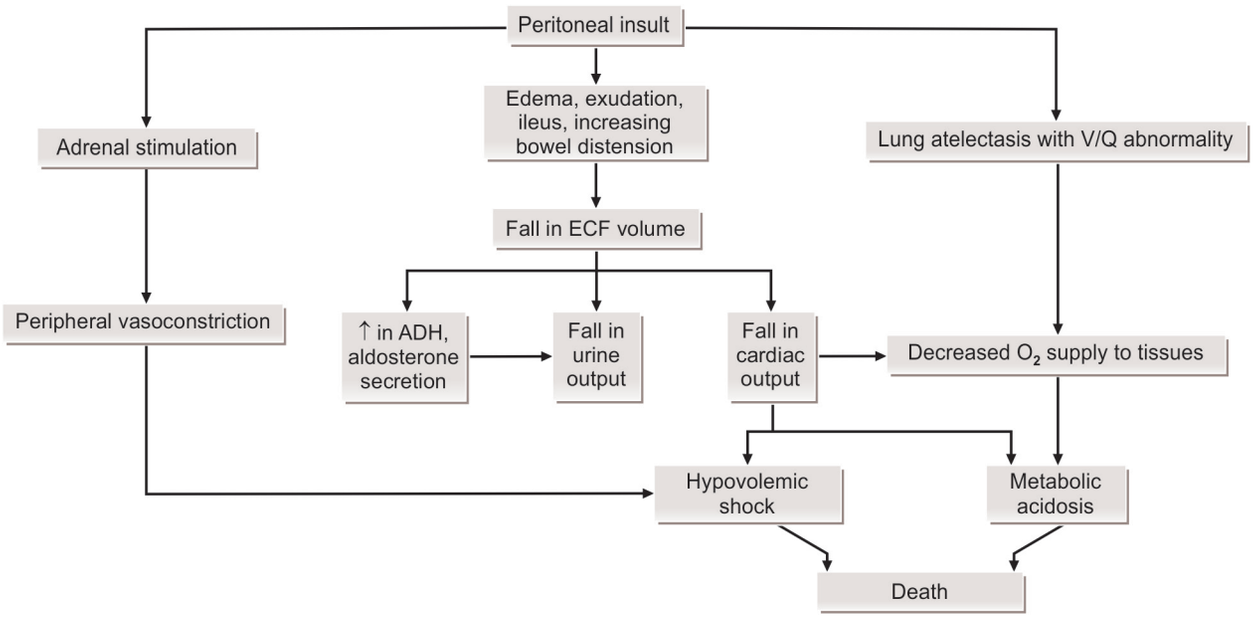
to achieve delivery of oxygen commensurate with the demand for oxygen by the tissues, resulting in tissue hypoxemia and lactic acid acidosis.

Protein catabolism is also increased from the very start, and progressively becomes more severe. Weight loss of 25–30% of lean body mass is observed if peritonitis persists. Though albumin synthesis is increased, serum albumin levels progressively fall, as albumin accumulates in the peritoneal cavity, and is lost to the general circulation.

If the above described general responses to suppurative peritonitis go unchecked, and if the hypovolemic circulatory state is uncorrected, there is increasing tissue hypoxia and increasing metabolic acidosis causing increasing dysfunction of all organ systems. Death results from irreversible hypovolemic shock. The classical clinical description of peritonitis by Hippocrates corresponds to this terminal hopeless state.

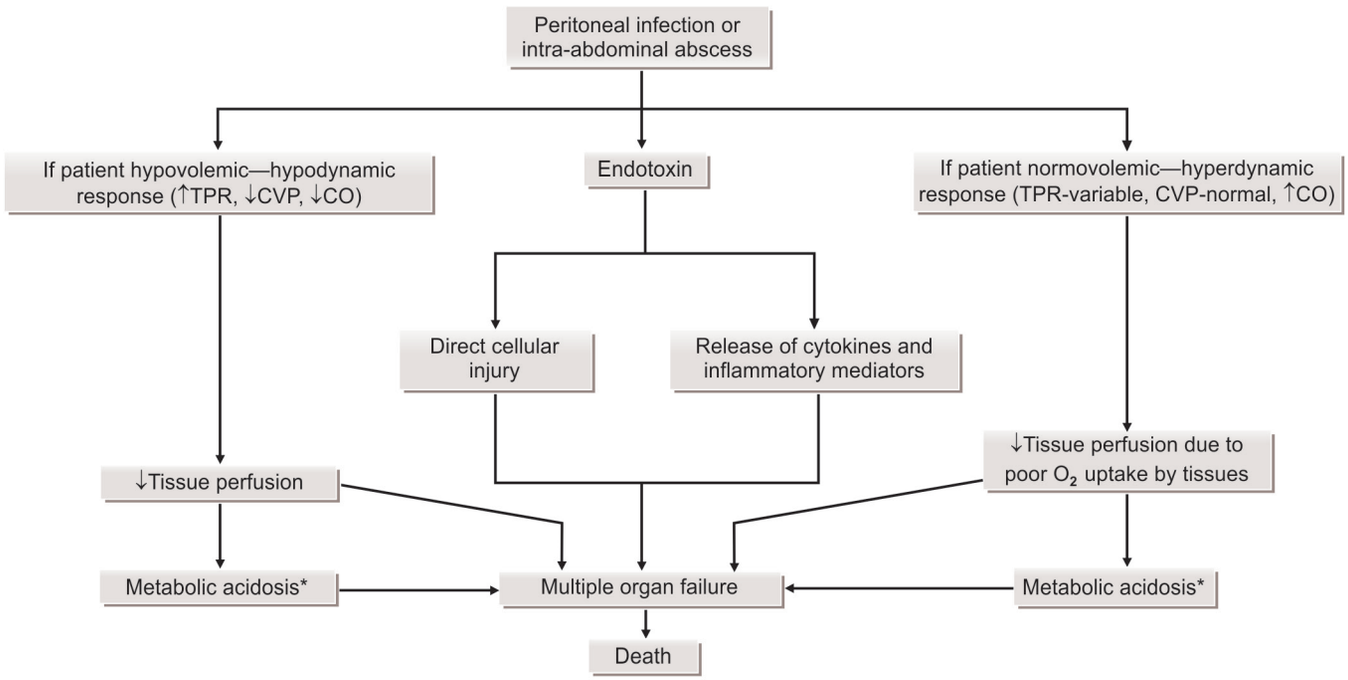
The general and specific responses to peritonitis are illustrated in Flowcharts 1 and 2.

Flowchart 1: General responses to peritonitis



Abbreviations: ECF, extracellular fluid; ADH, antidiuretic hormone; V/Q, ventilation/perfusion.

Flowchart 2: Specific responses to peritonitis


Peritoneal infection or intra-abdominal abscess
If patient hypovolemic—hypodynamic response (↑TPR, ↓CVP, ↓CO)
Endotoxin
If patient normovolemic—hyperdynamic response (TPR-variable, CVP-normal, ↑CO)
Direct cellular injury
Release of cytokines and inflammatory mediators
↓Tissue perfusion due to poor O_2 uptake by tissues
↓Tissue perfusion
Metabolic acidosis*
Multiple organ failure
Metabolic acidosis*
Death

*If early treatment successful, recovery possible.

Abbreviations: TPR, temperature, pulse, respiration; CVP, central venous pressure; CO, cardiac output.

Box 2: Factors determining severity of intra-abdominal sepsis

- Virulence and microbiology of pathogens
- Extent of contamination—
  - Maximal spillage in ileal and cecal perforation
- Presence of foreign bodies and blood
- Errors in management—
  - Unrecognized, unsutured perforations and leaks
  - Inadequate surgical drainage and debridement
  - Administration of laxatives in abdominal sepsis
- An immunocompromised patient
- Comorbid conditions—diabetes, chronic renal disease, cirrhosis of the liver, chronic alcoholism
- Elderly patients >70–75 years

Factors Determining Severity of Intra-Abdominal Sepsis (Box 2)

Virulence and Microbiology of Pathogens

The larger the dose of pathogens and greater their virulence, the more severe the infection. The microbiology of intra-abdominal sepsis is polymicrobial. This is always so when the peritoneal cavity is invaded from the GI tract. The most common bacteria are coliform organisms (mainly *Escherichia coli*), other *enterococci*, *Bacteroides fragilis*, anaerobic cocci and *Clostridia*. Other Gram-negative bacilli such as *Klebsiella* and *Proteus* species are often present, but form a small part of the total flora. There are an increasing number of fungal isolates in patients with prolonged sepsis and in immunocompromised hosts. Anaerobes always play an important role in contributing to the virulence of intra-abdominal and intraperitoneal sepsis. It is important to note that a patient in whom peritonitis or an intra-abdominal abscess develops in the hospital whilst on antibiotics may have a different aerobic flora. *Klebsiella*, *Proteus* and *Pseudomonas* often predominate, and may be resistant to antibiotics.

Extent of Contamination

The severity of peritonitis and intra-abdominal sepsis following spontaneous or traumatic perforation of the GI tract depends on the size and location of the perforation. Ileal or cecal perforations with spillage are associated with a greater contamination and greater morbidity than perforations of the very proximal or very distal parts of the GI tract. Proximally the gut has fewer bacteria, and distally the fecal contents are more solid, and the inflammation is more easily localized. On the other hand, ileal and cecal contents are liquid and have a high concentration of bacteria and of residual enzymes, which prevent localization of the infection.

Presence of Foreign Bodies and Blood

The presence of a foreign body or blood clots (which invariably get infected) increases the morbidity and mortality in peritoneal inflammation.

Errors in Management

The following errors need to be stressed, and should be avoided—

- Draining the peritoneal cavity at surgery, without also ensuring that all leaks from the GI tract or a ruptured viscus have been surgically sealed. A continuing source of peritoneal contamination always spells death.
- Attempting to control infection and sepsis by the use of antibiotics without adequate surgical drainage and debridement.
- An important error of commission is the administration of laxatives or enemas in abdominal sepsis. This increases the risk of rupture of an inflamed bowel segment.

Immunosuppressed Patients

Cancer, the prior use of antimitotic drugs, radiation therapy, myeloproliferative disease and human immunodeficiency virus (HIV) infection lead to a poor immune response to acute infection. The extent, gravity and prognosis of intra-abdominal sepsis are worse compared to immunocompetent patients.

Comorbid Conditions

The prognosis is comparatively poor when intra-abdominal sepsis occurs in uncontrolled diabetics, in cirrhotics, in alcoholics, in patients with chronic renal or heart failure and in the elderly.

CLINICAL FEATURES AND DIAGNOSIS[1,3]

The clinical features of intra-abdominal sepsis depend on the age of the patient, the background disease against which intra-abdominal infection develops, and whether the patient is immunocompetent or immunosuppressed.

Peritonitis presents as an acute abdomen, but localized suppuration (intraperitoneal abscess) may present with subtle manifestations.

Abdominal pain is the most important symptom of generalized peritonitis. It is severe and constant, the patient preferring to lie absolutely still in bed without any movement. Even turning in bed from one side to the other sharply increases the pain. To start with, the pain is maximal over the initial site of inflammation; it then spreads to involve the whole abdomen as generalized inflammation supervenes. Pain is often accompanied by nausea and vomiting.

The abdomen may show distension because of ileus. Abdominal movements on respiration are poor; the patient is tachypneic with shallow intercostal breathing. Tenderness on palpation, with guarding and rigidity, are accompaniments of peritoneal irritation and inflammation. Rebound tenderness is present; percussion of the abdomen is painful, and is merely a gentler method of eliciting rebound tenderness. Free fluid in the abdomen is difficult to detect on clinical examination, but is often present. Auscultation typically reveals a silent abdomen; the heart sounds are clearly heard on abdominal auscultation.

Table 1: Localized pain in the abdomen particularly if associated with a palpable tender "lump" helps to determine the intra-abdominal pathology

Right upper and middle quadrant	*Epigastric*	*Left upper and middle quadrant*
Acute cholecystitis Acalculous cholecystitis Hepatic abscess Hepatitis Cholangitis Pancreatitis Appendicitis (in pregnant women) Empyema of the gallbladder with obstruction to the cystic or common bile duct Pyelonephritis	Pancreatitis Pancreatic abscess Perforated peptic ulcer Mallory-Weiss syndrome Left lobe liver abscess Subphrenic abscess	Perforated peptic ulcer Pancreatitis Pancreatic abscess Splenic abscess Subdiaphragmatic abscess Pyelonephritis
Right lower quadrant	*Periumbilical*	*Left lower quadrant*
Acute appendicitis Acute salpingits Perforation of the cecum Pyelonephritis	Early acute intra-abdominal abscess Anastomotic leaks Abdominal compartment syndrome	Diverticular abscess Colonic perforation

Rectal examination and pelvic examination may reveal tenderness or a painful inflammatory mass. The hernial orifices and the genitals must always be inspected and examined.

Systemic features include fever, tachycardia, tachypnea and leukocytosis. None of these however may be present. Leukocytosis is generally observed but not always so. Leukopenia, if present, is of ominous significance.

Hypovolemic Shock

Clinical features of hypovolemia and hypovolemic shock are often present in the first few days of acute generalized suppurative peritonitis. This is, as explained earlier, due to sequestration of fluid from the interstitial tissue compartment into the peritoneal cavity and the lumen of the gut. Hypotension, tachycardia and oliguria with a rise in the nonprotein nitrogen and creatinine levels are observed. If the circulatory state is uncorrected and if prompt surgery for the peritonitis is delayed, the patient rapidly deteriorates and dies. The Hippocratic facies—"hollow eyes, collapsed temples, the color of the face brown, black, livid or lead colored"—is the description of a patient about to die with generalized peritonitis.

If on the other hand hypovolemia is corrected, the circulatory hemodynamics restored and critical care offered, the patient may proceed to develop all the features of prolonged sepsis. Sepsis may or may not respond to surgery and antibiotics. Sepsis will never respond if the cause or the source that seeds the peritoneum is undetected, or is not eradicated totally by surgical procedures. In patients with multiple bowel perforations, or in whom surgery has been delayed, or is inadequate, radical eradication of the sources of peritonitis is impossibly difficult. The very friable bowel loops with total obliteration of tissue planes render the approach to the sites of perforation impossible. Death from multiple organ failure is inevitable in these patients. The better the critical care offered, the slower and more agonizing the death, particularly so in young patients. It is pathetic to helplessly watch the slow decline, and the final inevitable disintegration of all organ system functions in these patients.

Localized Peritoneal and Retroperitoneal Inflammation

In the form of an intra-abdominal abscess, localized peritoneal and retroperitoneal inflammation may show few or no clinical signs. A tender localized mass is not always palpable. A subphrenic abscess may present with dyspnea, hiccups, referred shoulder pain, basal atelectasis or pleural effusion. A pelvic abscess may present with diarrhea or urgency of micturition. A rectal and vaginal examination may elicit tenderness, by causing direct pressure over the inflamed mass or peritoneum. A psoas abscess may manifest as spasm and pain in the hip, when the psoas is stretched on extension of the hip (the psoas sign). Retroperitoneal perinephric abscesses are difficult to diagnose clinically till the abscess surfaces and produces warmth and tenderness over the loin posteriorly.

Systemic features include fever, often spiky in nature and leukocytosis. If the abscess is undrained, sepsis is protracted, and leads to progressive multiple organ dysfunction, failure and death (see Chapters Multiple Organ Dysfunction Syndrome and Sepsis and Septic Shock).

Localized pain, tenderness, guarding over different quadrants of the abdomen (particularly when associated with a lump) often point to the site of the abdominal pathology. Table 1 is not all-inclusive in this regard but illustrates the above point.

The diagnosis of intra-abdominal sepsis is particularly difficult in the following groups of patients—

1. *In the immunosuppressed patient*, inflammatory reactions and all immune responses are suppressed or muted. The usual abdominal signs may be barely elicitable.

This is particularly so in severely neutropenic patients. The presence of fever of undetermined origin in these patients should prompt a meticulous search for possible abdominal sepsis. Imaging studies are of great help in arriving at a correct diagnosis.

2. *In patients who are critically ill in the ICU*[3-5] for unrelated problems, but who develop intra-abdominal sepsis as a complication, intra-abdominal sepsis may be fortuitous or iatrogenic (as for example, peptic perforation in a patient on corticosteroids). It may also occur as a complication of a poor perfusion state or a low output syndrome. This can cause bowel ischemia, a small leak from the bowel and intra-abdominal suppuration. Acalculous cholecystitis or acute pancreatitis can also occur as a complication of a low output syndrome or due to poor perfusion of the abdominal viscera. Intra-abdominal suppuration could also result from an anastomotic leak in an operated patient receiving postoperative surgical care, or from a fortuitously occurring abdominal pathology unrelated to the primary illness.

   Recognition of intra-abdominal suppuration is difficult because of the paucity of symptoms and physical signs, the preoccupation of the intensivist with the primary critical illness for which the patient is admitted, and because of the frequent presence of a blunted sensorium in a very ill patient. The use of analgesics, in particular opioid analgesics, antibiotics, and of mechanical ventilator support in a critically ill individual, renders the diagnosis of a life-threatening abdominal pathology doubly difficult. The history is not likely to be contributory in an obtunded patient. It retains its importance if the patient is alert and can describe the nature and site of pain, and can help the examining physician to localize the site of pain or confirm its generalized nature on abdominal palpation. Abdominal examination in suspected intra-abdominal suppuration in a critically ill individual should be performed serially. A digital rectal examination should always be done; a vaginal examination for suspected pelvic sepsis is also important. Since abdominal pain for various reasons may be difficult to evaluate in a critically ill patient, an overall concern with other clinical features may point to possible intra-abdominal sepsis. The occurrence of a new fever, increasing tachycardia, tachypnea should arouse suspicion for an occult abdominal pathology. Patient-ventilator asynchrony, an increased respiratory rate, a rise in peak inspiratory pressure may be features of a metabolic acidosis consequent to abdominal sepsis. Abdominal distension, absent bowel sounds, an increase in the nasogastric aspirate, inability to tolerate nasogastric feeds are tell-tale features of possible mischief in the abdomen. Increase in bowel movements may signal infection with *Clostridium difficile*. Change in quantity or character of the drainage fluid from an intra-abdominal drain after surgery should arouse suspicion of a possible anastomotic leak. Increased discharge from the operated wound should suggest wound dehiscene from infection. A delay in diagnosis of an acute abdomen or intra-abdominal sepsis in a critically ill patient is associated with an increased mortality.
3. *In the immediate postoperative patient*, intra-abdominal sepsis including peritonitis is difficult to diagnose if it occurs as a complication in a patient who has been operated upon very recently. This complication again may be fortuitous or iatrogenic (chiefly as a result of perforation of the bowel during surgery). The pain of the surgical wound is not immediately distinguishable from the pain of peritonitis. The persistence of paralytic ileus after surgery should always suggest an underlying perforation with peritonitis or a localized abscess within the abdominal cavity. Physical signs of tenderness, guarding and rigidity are often difficult to evaluate in these patients in the immediate postoperative period. When perforation of the gut with peritonitis occurs soon after a cesarean section for a full-term delivery, the diagnosis is doubly difficult. The stretched abdominal muscles (as a result of pregnancy) show minimal guarding and little or no rigidity. A history of sudden pain in the abdomen a few days after surgery, the presence of ileus, rebound tenderness and the demonstration of free fluid within the abdomen should point to the correct diagnosis.

DIFFERENTIAL DIAGNOSIS[3,4]

The differential diagnosis of intra-abdominal sepsis is extensive and includes all other causes of acute abdomen—in particular acute bowel obstruction, acute bowel ischemia, pancreatitis and a ruptured ectopic pregnancy in a female patient. An intra-abdominal abscess may masquerade as systemic sepsis, the source of which is undetermined. In patients with cirrhosis of the liver, primary peritonitis needs to be distinguished from peritonitis secondary to perforation or inflammation of the abdominal viscera.

Acute medical problems may present with acute abdominal pain and tenderness in the abdomen, and mimic intra-abdominal inflammation due to surgical pathologies. The most important of these problems are acute pneumonia which produces referred pain in the upper abdomen and at times even in the right iliac fossa, and acute viral hepatitis which can produce generalized abdominal pain, pain in the right iliac fossa and pain in the right upper abdomen. This is particularly observed in children and in young adults. Acute myocardial infarction may mimic a surgical abdomen if it presents with severe epigastric pain, vomiting or shock. Acute falciparum malaria can also present with severe abdominal pain. The latter is also a classic feature of severe diabetic ketoacidosis. The importance of a routine urine examination cannot be overemphasized. Acute glomerulonephritis in children often present with abdominal pain or severe loin pain. Acute exanthemas in children often present with fever and generalized or even localized abdominal pain. The diagnosis is apparent with the appearance of a characteristic skin rash. Finally, other rare but important causes of severe abdominal pain (not generally associated with rigidity or

Box 3: Important medical conditions that can mimic an acute abdomen

- Pneumonia (referred pain in abdomen)
- Acute hepatitis
- Acute myocardial infarction—presenting with severe abdominal pain and vomiting
- Dengue (intra-abdominal bleed)
- Acute exanthemas in children
- Diabetic ketoacidosis
- Acute glomerulonephritis—particularly in children
- Uremia
- Acute adrenal insufficiency
- Acute falciparum malaria
- Acute sickle cell crisis
- Acute porphyria
- Acute enterocolitis

rebound tenderness) are acute porphyria and acute adrenal crisis. Box 3 gives a list of important medical conditions that can mimic an acute abdomen.

Laboratory Findings

Blood examination should include a complete blood count, platelet count, erythrocyte sedimentation rate (ESR), serum electrolytes, liver function tests, blood sugar, blood urea and serum creatinine. Systemic features of sepsis should warrant investigations for the coagulation profile, arterial blood gas analysis, blood lactate, procalcitonin level and tests to evaluate functions of different organ systems. A routine urine examination together with cultures of blood, urine and peritoneal fluid are important investigations before starting empiric antibiotic therapy.

Marked leukocytosis spells acute infection and/or suppuration. Severe leukopenia can also be a feature of sepsis. It is important to obtain a differential cell count to see if there is shift to the left. In a critically ill individual, a sharp sudden rise in bilirubin might signify an acute acalculous cholecystitis. A rise in amylase and lipase points to pancreatitis. An isolated rise in amylase can also occur in a perforated viscus, bowel obstruction or ischemic bowel. A sharp rise in bilirubin, transaminases, alkaline phosphate may point to a pathology in the liver and biliary tree. Increased blood lactate generally occurs with sepsis and tissue hypoxia. Abdominal compartment syndrome should be suspected when acidosis, hypoxemia, distended abdomen and oliguria are present. A bladder pressure greater than 30 mm Hg may warrant urgent surgical decompression.

Imaging Studies[6,7]

These are of crucial importance in the diagnosis of intra-abdominal inflammation, as also in the differential diagnosis of other causes of acute abdomen.

An X-Ray of the Chest (If Possible in the Upright Posture)

This can exclude pneumonia as a cause of acute abdominal pain and fever. Gas under the diaphragm is indicative of a perforated viscus. Intra-abdominal suppuration often causes elevation of one or both domes of the diaphragm and basal atelectasis.

Pleural effusion is an important finding in a subphrenic abscess or in acute pancreatitis.

An X-Ray of the Abdomen (AP) in the Erect Posture[6,7]

Gas under the diaphragm is indicative of perforation of a hollow viscus. Fluid levels, often in a step-ladder fashion, point to an intestinal obstruction. Small bowel or large bowel obstructions can be diagnosed from the pattern of the bowel proximal to the obstruction. Three or more fluid levels in the abdomen should be considered significant, and point to some degree of obstruction within the gut. A follow-up X-ray needs to be done in such patients after some hours. Paralytic ileus, whether due to medical or surgical problems, is characterized by marked distension of the small gut. This may involve the colon as well. Acute dilatation of the stomach is demonstrated by the outline of a hugely distended stomach, with an air-fluid level.

If perforation of a viscus is suspected, and the patient is too ill for an X-ray in the erect posture, then a left lateral decubitus X-ray of the abdomen (with the left side down) is of help. It may show the presence of free air between the liver margin and the abdominal wall. An X-ray of the chest or abdomen with the patient in the supine posture may not yield this crucial information, and may therefore be misleading.

Presence of free fluid and gas in the peritoneal cavity after perforation of the gut is visible as a fluid collection (generally gravitating into the pelvis), with a clear horizontal air-fluid level.

Rarer findings in intra-abdominal suppuration on a plain X-ray include: (1) air in the wall of the gut—pneumatosis intestinalis is observed in some patients with gangrene of the gut; (2) air in the gallbladder lumen in patients with empyema caused by gas forming organisms; (3) thumb-printing of the colonic wall in ischemic colitis; (4) marked distension of the colon in megacolon and in Ogilvie's syndrome. The latter occurs after surgery, and is characterized by severe ileus involving the large bowel. Cecal distension may lead to perforation and peritonitis in some patients.

Ultrasonography of the Abdomen[6,7]

This is a portable, noninvasive useful diagnostic tool. It is of special value in diagnosing acute cholecystitis, cholangitis or stones in the gallbladder. Ultrasonography is useful in the diagnosis of acute pancreatitis, pancreatic fluid collections, intraperitoneal and retroperitoneal abscesses, pelvic abscesses, pelvic tumors and ruptured ectopic pregnancy.

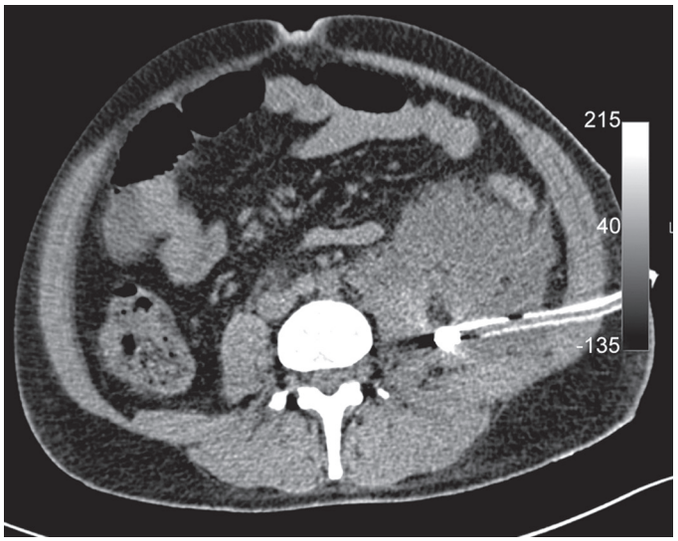


Fig. 1: CT abdomen shows a drainage tube in situ in the left lumbar region within a fluid collection as a result of pancreatic sepsis

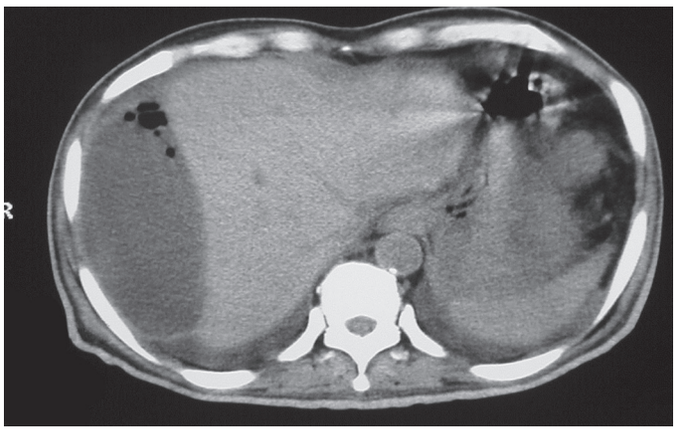


Fig. 2: Abdominal sepsis—CT of the abdomen reveals a large sub-phrenic fluid collection with specs of air within

Unfortunately, the sensitivity of an ultrasound examination is lost or vitiated to an extent, by the presence of overlying gas in the bowel, by skin incisions and bulky dressings over surgical wounds. The presence of an ileostomy, colostomy or open wounds limits the use of this otherwise extremely valuable diagnostic investigation.

Computed Tomography Scan[6]

A computed tomography (CT) scan (Figs 1 to 3) is more sensitive and specific than an ultrasound for identification of abscesses within the abdomen (intraperitoneal, retroperitoneal or within a viscus). It is particularly useful for the correct diagnosis of pancreatic necrosis or pancreatic and peripancreatic suppuration. The sensitivity of a good CT scan of the abdomen approaches 95–100%.

Gastrografin Studies

Oral gastrografin is sometimes used in patients with intestinal obstruction to determine the site of a small bowel obstruction

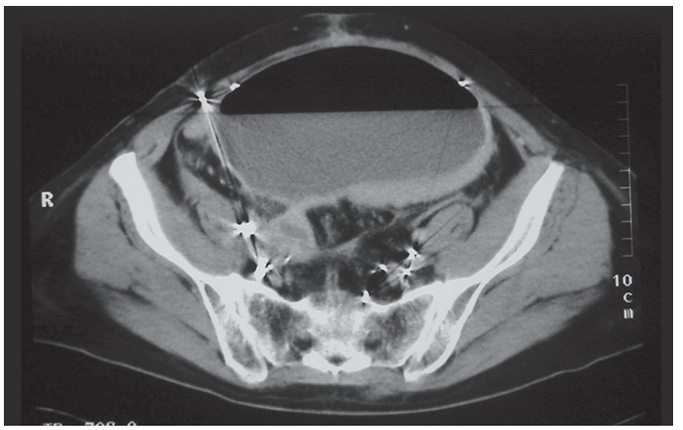


Fig. 3: Abdominal sepsis—CT scan of the abdomen reveals a large fluid collection in the mid-abdomen with an air fluid level

just before surgery. If a patient operated upon for a perforation of the gut fails to improve and shows continuing sepsis, it probably indicates the presence of one or more other perforations or the formation of a new intra-abdominal abscess. Oral gastrografin can demonstrate a perforation with a leak of the dye in the peritoneal cavity, or can outline the anatomic site of an enteric fistula.

Gastrografin given rectally helps to distinguish between a terminal ileal obstruction and a proximal colonic obstruction.

Angiographic Studies

Acute intra-abdominal suppuration is sometimes associated or complicated by massive bleeds. This is particularly observed with suppurative pancreatitis which can cause bleeds within the gut or outside it. Most patients are generally too ill for open exploratory surgery to stop such bleeds. The distortion of tissue planes also often makes this task impossibly difficult. Angiographic studies with the catheter placed in the appropriate vessels can demonstrate the bleeding vessels, which can then be suitably embolized with gelfoam coil or other agents. CT angiographic studies are invaluable in the diagnosis of occlusion of the mesenteric vessels causing bowel ischemia and gangrene.

MANAGEMENT[3-5,8,9]

Management consists of the following important features—

- Quick restoration of the circulatory hemodynamics.
- Source control—surgical intervention is invariably necessary.
- Prompt use of antibiotic therapy.
- Critical care and support of different organ systems.
- Maintenance of nutrition.

Management Prior to Surgery

Restoration of Circulatory Hemodynamics

Most patients are hypovolemic from the massive sequestration of fluid into the peritoneum and into the lumen of the gut.

Intravenous infusions of normal saline, dextrose saline and Ringer lactate solutions should be given to raise the central venous pressure (CVP), the filling pressures of the ventricles and the cardiac output. Vasopressor and inotropic support may be necessary (see Chapter Sepsis and Septic Shock). Intake/output charts are carefully maintained. All vital signs, the arterial blood pressure in particular, are also carefully monitored. Abnormalities in electrolyte balance and acid-base equilibrium should be corrected. The hemoglobin should be raised by packed cell infusions and kept close to 10 g/dL. Deranged clotting mechanisms should be corrected by infusions of fresh frozen plasma.

Too rapid infusions in patients with overt cardiac dysfunction can cause pulmonary edema. *Over-resuscitation of shock can cause hypervolemia, and should be avoided as this can precipitate the subsequent development of acute respiratory distress syndrome (ARDS).*

Antibiotic Therapy[10]

(See Chapter Antibiotic Therapy in the Intensive Care Unit)

Empiric therapy should be promptly started, especially in critically ill patients (within 1 hour) after relevant cultures have been sent. One should never await culture results before starting therapy. Cultures of infected material should also be sent during surgery; the empiric antibiotic regime may need modification depending on these results.

The empiric regime that is chosen for IAIs depends chiefly on—

- Presumed/Identified source of infection.
- Presumed pathogens involved, the risk factors for likely major resistant patterns and the prevailing antibiotic sensitivity in the unit.
- The severity of the patient's illness.

Risk factors include high severity of the illness, age more than 70 years, co-morbidities, high level of antibiotic exposure, poor nutritional state, underlying cancer.

IAIs are invariably polymicrobial. Major pathogens in community acquired IAIs are Enterobacteriaceae, Streptococcus spp. and anerobes (chiefly B. fragilis). The spectrum is broader in nosocomial infections and further includes enterococcus, Kl. pneumoniae, Ps. pyocyaneus and Acinetobacter baumannii.

Multidrug resistant infections are invariably present in critically ill patients with nosocomial infection. Unfortunately the level of resistance due to increased prevalence of ESBLs in community acquired infections is also on the rise.

The antibiotic regimes are best considered under the following three heads—

I. Extrabiliary Community Acquired IAIs.
II. Biliary Community Acquired IAIs.
III. Nosocomial IAIs.

The regimes we use as per our antibiotic sensitivity results are given below.

I. Extrabiliary Community Acquired IAIs:
   A. Patients not critically ill; no risk factors for ESBL.
      Amoxicillin clavulanate or Ceftriaxone
   B. Patient not critically ill; risk factors for ESBL present.
      Amoxicillin clavulanate + Tigecycline
   C. Patient critically ill (i.e. severe sepsis or septic shock) but no risk factors for ESBLs.
      Piperacillin tazobactam
   D. Patient critically ill + risk factors for ESBLs.
      Meropenem/Imipenem + Tigecycline + Fluconazole

II. Biliary Community Acquired IAIs:
   A. Patients not critically ill; no risk factors for ESBLs.
      Amoxicillin clavulanate or cefoperazone sulbactam
   B. Patient not critically ill; risk factors for ESBLs present.
      Tigecycline
   C. Patient critically ill (i.e. severe sepsis or septic shock) but no risk factors for ESBLs.
      Piperacillin tazobactam
   D. Patient critically ill + risk factors for ESBLs present.
      Piperacillin tazobactam + Tigecycline + Fluconazole

III. Antibiotic therapy for hospital acquired infections.
   Piperacillin tazobactam + Tigecycline + Echinocandins or Meropenem/Imipenem + Tigecycline + Echinocandins

Fungal infections should always be suspected and covered in critically ill patients with IAIs. Echinocandins are preferred to fluconazole in severe nosocomial IAIs.

Definitive Surgical Treatment[11,12]

Surgery

The definitive treatment of IAIs lies in the surgical eradication of the septic focus and debridement of necrotic tissue. Surgery should not be unnecessarily delayed. In some patients a single operation may not be sufficient to achieve source control. A re-laparotomy may be needed. Three methods of surgical management of severe IAIs following initial laparotomy are currently debated—(1) open abdomen, (2) planned laparotomy and (3) on-demand laparotomy. Currently on-demand (i.e. only when felt necessary) laparotomy is the preferred method as it results in a reduction of laparotomies and in medical cost.

Percutaneous Drainage of Abscesses[13]

Well-localized peritoneal or retroperitoneal abscesses that are easily accessible by percutaneous needle aspiration, can be drained in this fashion. Repeated aspirations can be done under ultrasound or CT guidance, or preferably, a large bore pigtail drain or a sump catheter is placed in the abscess cavity, again under ultrasound or CT guidance. The abscess cavity can than be intermittently irrigated with normal saline and appropriate antibiotics. The drain is removed when the drainage ceases and when the abscess cavity appears obliterated on a CT scan or a sinogram. Percutaneous drainage is obviously not to be used if the abscess cavity contains thick pus or a significant quantity of necrotic material. Drainage through a pigtail or sump catheter is likely to be unsuccessful if there are multiple pockets of pus. If the response to percutaneous drainage is inadequate, open surgical drainage with debridement of necrotic tissue should be performed.

Critical Care[8,9]

This is vital both during the preoperative and postoperative stages. Attention to *fluid, electrolyte and acid-base balance, and to nutrition* are vital. *Cardiorespiratory support* and, in particular, *ventilator support* are invariably necessary in critically ill patients. Hemodynamic monitoring which includes an arterial line and in complicated problems the insertion of a Swan-Ganz catheter may be necessary. Antibiotics may need to be continued for 2 weeks or even longer in some patients.

Persistent sepsis after abdominal surgery indicates one or more of the following—

1. An undetected perforation of the gut or a new perforation.
2. A postoperative intra-abdominal abscess.
3. The presence of devitalized gut due to ischemia involving a segment of the bowel.
   A rising bilirubin with a rise in liver enzymes following abdominal surgery for a perforation suggests that factors (1) and (2), or both in combination, are possibly present as postoperative complications.
4. An ongoing peritoneal infection often due to resistant organisms.
5. *Fungal infection* The occurrence of a superadded fungal infection should always be considered in unresolved intra-abdominal sepsis, particularly in immunocompromised patients or in those who have received prolonged broad-spectrum antibiotic therapy. The discharge from wounds, fistulae, should always be sent for fungal culture. Blood cultures for fungal infection may be positive even when discharge from the area of suppuration is negative. Appropriate antifungal treatment is life-saving in fungal infections.
6. *Nosocomial infection* (wound infection by resistant bacteria, pneumonia, catheter-related sepsis, urinary tract infections).

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CHAPTER 51

Abdominal Compartment Syndrome

INTRODUCTION

The abdominal cavity is a space defined partly by rigid structures such as the spine, pelvic bones, costal arches, and partly by flexible structures, such as the abdominal muscle wall and the diaphragm. The intra-abdominal contents are limited by these anatomical boundaries. If there is a discrepancy between the total volume of the intra-abdominal contents (sum total of viscera, fluid, vessels) and the anatomical space limited by the boundaries described above, intra-abdominal pressure (IAP) rises. This predicament could occur if there is a marked increase in the total volume of intra-abdominal structures (swelling of viscera or accumulation of fluid) or decreased space within the abdominal cavity. In clinical medicine, it is the increase in volume of the total intra-abdominal contents within a confined space that leads to increased IAP.[1] To start with the stretch of the flexible boundaries of the abdominal compartment accommodates the increased volume of the intra-abdominal contents. Once the limits of accommodation are reached, even a small rise in the volume of intra-abdominal contents will produce a sharp rise in pressure. There is considerable work to show that increasing IAP can have a deleterious effect on organ function and can contribute significantly to multiorgan failure.

DEFINITIONS WITH REGARDS TO VARIOUS DEGREES OF RISE IN INTRA-ABDOMINAL PRESSURE

- *Normal intra-abdominal pressure* The normal IAP is measured in the supine position and is less than 10 mm Hg.[2]
- *Elevated intra-abdominal pressure* Intra-abdominal hypertension (IAH) is defined as a peak pressure more than or equal to 12 mm Hg on taking two measurements 1–6 hours apart.[2]
- *Abdominal compartment syndrome* Abdominal compartment syndrome (ACS) is diagnosed when (1) the peak IAP is more than or equal to 20 mm Hg on two successive measurements 1–2 hours apart, and (2) there is one or more organ failure not previously present, as defined by a sequential organ failure assessment (SOFA) score of more than or equal to 3.[2]

The ACS is of three types: (1) primary, (2) secondary and (3) tertiary. The consensus definitions of these three types are given below—

1. *Primary ACS* is that caused by intra-abdominal or pelvic pathology usually requiring abdominal surgery and/or angioradiologic intervention. The pathology may be traumatic and/or inflammatory in nature.[2]
2. *Secondary ACS* is ACS that is due to increased volume of intra-abdominal contents—fluid, swelling of viscera, and not due to an intra-abdominal pathology requiring surgery or angioradiologic intervention. Secondary ACS is observed during massive fluid resuscitation for major nonabdominal/pelvic injury, burns, acute pancreatitis and septic shock arising from nonabdominal and nonpelvic infections.
3. *Tertiary ACS* refers to ACS that develops or persists despite attempts to prevent or treat primary or secondary ACS.

Hyperacute ACS is a term used for very early secondary ACS that develops when surgery or angioradiological control of an injury is carried out simultaneously with massive resuscitation for the shock caused by the same injury.[3]

MEASUREMENT OF INTRA-ABDOMINAL PRESSURE

The IAP is measured indirectly by measuring the intravesical pressure. The recommended technique is to clamp the urinary catheter and instill 25 mL of sterile room temperature saline into the bladder, with the patient lying supine. After zeroing the transducer and allowing 30–60 seconds for stabilization the mean IAP can be read on a bedside monitor or as the height of the column in the urinary drainage tubing.

PATIENTS AT RISK FOR DEVELOPING ABDOMINAL COMPARTMENT SYNDROME[1]

These chiefly include—

- Patients with severe sepsis, particularly those with severe abdominal sepsis.
- Patients undergoing massive fluid resuscitation, whatever the cause—chiefly sepsis, trauma.
- Patients with acute pancreatitis, bowel gangrene.
- Patients with severe burns needing resuscitation with large volumes of fluid.

It is recommended that all patients falling in the above categories should be closely monitored for the development of ACS.

CLINICAL FEATURES[4,5]

- Increased pressure in the intra-abdominal cavity high enough to cause the ACS progressively impairs organ function.
- The first organ to be affected is the kidney, and the first clinical feature is a progressively falling urine output with a rising creatinine. This is due to a fall in renal perfusion, and reduced glomerular filtration. There is also an increase in renal venous pressure.
- The cardiovascular system is quick to suffer. The increased IAP leads to compression of the inferior vena cava, reduced venous blood flow to the heart with a reduced cardiac output. The fall in cardiac output affects the oxygen supply to all body tissues and probably plays an important role in evolving multiple organ dysfunctions. The filling pressure as measured from the central venous line may be falsely elevated because of both increased intra-abdominal and intrathoracic pressure.
- The respiratory system changes are characterized by increasing intrathoracic pressures, decreased lung volumes, decreased compliance and decreased alveolar ventilation. Respiratory failure with hypoxia and hypercapnia results.
- The gastrointestinal system is also markedly affected. The increased IAP leads to a fall in splanchnic perfusion, a fall in mucosal perfusion with the formation of mucosal erosions and ulcers. There is bacterial translocation which worsens organ dysfunction and failure.
- Liver functions are adversely affected because of the high IAP reducing both portal vein flow and hepatic flow. Glucose metabolism, mitochondrial function and cytochrome p50 function are all impaired.
- The central nervous system is also indirectly affected by the high IAP. The intracranial pressure is increased (largely due to an increased intrathoracic pressure) and the cerebral perfusion pressure is reduced.
- Multiorgan failure results from (1) the primary pathology and the treatment that causes the ACS; (2) tissue hypoperfusion and hypoxia caused by the cardiovascular and respiratory effects of the ACS; (3) a hypothesis has been postulated that the ACS itself acts as a proinflammatory stimulus in patients already primed by the primary pathology that resulted in ACS.[8]
- Studies have illustrated the association between ACS and multiple organ dysfunction syndrome (MODS).[6] Some workers believe that the increased bacterial translocation caused by ACS induced ischemia to the gut may play an important role in an evolving MODS.

TREATMENT[1,4,6]

The optimal treatment is abdominal decompression by surgery in all patients where the high IAP is associated with evidence of organ dysfunction. Following abdominal decompression there is a quick improvement in hemodynamic and respiratory parameters with improvement in tissue perfusion and oxygenation. After decompression, intravascular volume should be maintained. It is advisable to use vasoconstrictor agents to avoid fluctuations in blood pressure and to prevent reperfusion injury from the washout of the by-products of anaerobic metabolism. Following decompression the abdomen is left open, using one of the methods to later allow temporary abdominal closure.

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SECTION

15

Organ System Dysfunction Requiring Critical Care

- Multiple Organ Dysfunction Syndrome
- Acute Kidney Injury
- Critical Care in Acute Hepatic Failure
- Acute Pancreatitis
- Acute Gastrointestinal Bleeding
- Hemorrhagic Disorders
- Transfusion (Blood Product) Therapy
- Endocrine Dysfunction
- Diabetes Mellitus
- Neurological Problems

CHAPTER 52

Multiple Organ Dysfunction Syndrome

INTRODUCTION

The multiple organ dysfunction syndrome (MODS) (also called multiple organ failure) has gained increasing importance over the last 30 years. It remains even today one of the major therapeutic challenges faced by physicians treating patients with critical illnesses due to widely differing etiologies. Single organ failure was long recognized as an important cause of morbidity and mortality in surgical patients. In the late 1960s, extended organ failure sequentially involving the lungs, liver and kidneys, and finally resulting in death, was observed in patients suffering from severe trauma. In 1973, Tilney and colleagues reported on a case of failure of multiple organ systems causing death, following the repair of a ruptured aortic aneurysm.[1] The syndrome of multiple organ failure as a distinct nosologic entity was increasingly recognized in the 1980s,[2] and today it is rightly considered as an unsolved problem carrying a forbidding mortality in ICUs all over the world.

What is the reason for the increasing incidence of this frightening entity over the last three decades? Ironically enough, the recognition and increasing incidence of this syndrome is to an extent related to better critical care in the early phase of a severe illness—critical care which enables the patient to weather the initial storm, and not succumb to it. It is only against such a background, where very ill patients are expertly cared for and supported over a period of time (this being virtually impossible 40 years ago), that the syndrome of multiple organ dysfunction or failure unfolds. In other words, this syndrome is a product of "progress" in critical care, and "progress" in life-saving technology.

The syndrome of multiple organ failure illustrates perfectly the interdependence of different organs of the body—an idea that was intuitively grasped by the ancient Ayurvedic physicians in India. The syndrome also illustrates the fact that no organ functions in isolation, that each organ influences the other, and that deranged function in one has far-reaching effects on the other organs. It is this harmony of the whole, rather than the function of individual parts, which spells the difference between health and disease, as also between survival and death.

DEFINITION AND CONCEPT

There is as yet no precise definition of multiple organ failure. Clinically, it can be considered as the sequential or concomitant occurrence of severe derangement of function in multiple organ systems of the body, against a background of a critical illness. Various serious illnesses can induce multiple organ failure, the commonest and most frequent being sepsis, trauma and shock from any cause. The syndrome semantically has been given various name—sequential organ failure,[3] multiple organ failure[4] and multiple system organ failure (MSOF).[5] For reasons stated below, and in agreement with the recommendations of an ACCP/SCCM Consensus Conference on the subject,[6] the term multiple organ dysfunction syndrome is to be preferred.

The difficulty in precise definition is directly related to defining what failure of function exactly means or signifies in various organ systems of the body. Parameters of one or more organ system failure vary with different investigators. The variability of indices constituting organ failure in different studies prevents a correct interpretation and comparison between mortality figures and the effects of treatment. There is yet no universally acceptable classification system which defines parameters of organ specific failure. Knaus and colleagues[7-9] developed an Acute Physiologic and

Chronic Health Evaluation Score II (APACHE II) system, which is considered by many to be a significant advance in this direction. The APACHE II scoring system gives precise measurements of organ-specific failure in five systems: (1) the cardiovascular, (2) pulmonary, (3) renal, (4) neurologic and (5) hematologic systems.

Since the initial description of the APACHE II system, there has been an increasing awareness of the role of the liver in multiple organ dysfunction and failure. Precise measurements defining severe liver cell dysfunctions have therefore also been incorporated recently in the APACHE II score.[9]

A modified APACHE II criteria for organ system failure, which purports to define failure of each specific organ system, is given in Box 1.

In our opinion, the usefulness of the above system lies only in predicting ICU outcome. It merely forecasts a very high mortality when three or more organ systems have failed for more than 3 days. Even in this prognostication, there are, as will be discussed later, certain important exceptions that need to be carefully considered.

The APACHE III scoring system is a refinement of the APACHE II. Analysis of the APACHE III database of 17,440 patients indicates that a consideration of the features of the acute disease together with detailed physiological mapping perhaps provides better estimates of ICU mortality than the number of organs termed "dysfunctional". Also, different combinations of organ dysfunction could result in differing mortality. Thus, mortality was 20% in patients with cardiovascular and hematological dysfunction vis-à-vis 76% in those with cardiovascular and neurological dysfunction.

There are important lacunae in our present-day concept of the MODS and these lacunae are briefly discussed below—

1. The major criticism is that the parameters defined above take into consideration failure of an organ system at only one point in time, when the disease process is perhaps too advanced to respond to treatment. The syndrome of multiple organ failure is in reality a dynamic ongoing process, so that consideration of disturbed function, without reference to the tempo and natural course of the disease, is unsatisfactory.

   Each organ system in this syndrome has to tread a path of increasing dysfunction that can end in terminal failure, from which there is no return. Organ dysfunction may be mild, moderate or severe. Multiple organs may show varying dysfunction. The recognition and significance of early organ dysfunction is not just of academic interest; it may help to initiate treatment at an early stage in the natural history of the syndrome. It is important to test specific variables of function (both singly and in groups or combinations) of different organ systems against outcome. This concept should perhaps be mirrored semantically by using the term multiple organ dysfunction, rather than multiple organ failure. An ACCP or SCCM Consensus Conference, which was held in 1991, defined MODS as the *presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention*.[6] We strongly concur with this definition.
2. A summative conceptual model of organ system dysfunction which merely stresses the number of organs that have critically failed at one given point in time (as in the APACHE II system) is only of statistical prognostic value. It is relevant to consider varying degrees of dysfunction (from the mild to the hopelessly irreversible) in each organ system, at different points in time in the natural history of a critical illness, as also to consider, if possible, the inter-relation between these failing organ systems. The Sequential Organ Failure Assessment System (SOFA score) offers a more clear insight and a more practical and realistic concept for predicting mortality in MODS[10] (Table 1).
3. The definition of organ failure is problematic in certain organ systems. Thus, one could accept varying degrees

Box 1: Modified APACHE II criteria for organ system failure*

Cardiovascular failure (presence of one or more of the following)—
- Heart rate ≤54/min
- Mean arterial blood pressure ≤49 mm Hg (systolic blood pressure ≤60 mm Hg)
- Occurrence of ventricular tachycardia and/or ventricular fibrillation
- Serum pH ≤7.24 with a $PaCO_2$ of ≤40 mm Hg

Respiratory failure (presence of one or more of the following)—
- Respiratory rate ≤5/min or >49/min
- $PaCO_2$ ≥50 mm Hg
- $(A\text{-}a)O_2$ ≥350 mm Hg
- Dependent on ventilator or CPAP on the 2nd day of OSF (i.e. not applicable for the initial 24 hr of OSF)

Renal failure (presence of one or more of the following)†—
- Urine output ≤479 mL/24 hour or ≤159 mL/8 hour
- Serum BUN ≥100 mg/100 mL
- Serum creatinine ≥3.5 mg/100 mL

Hematologic failure (presence of one or more of the following)—
- WBC ≤1000/mm^3
- Platelets ≤20,000/mm^3
- Hematocrit ≤20%

Neurologic failure—
- Glasgow Coma Score ≤6 (in absence of sedation)
- Glasgow Coma Score: sum of best eye opening, best verbal, and best motor responses (for Glasgow Coma Scale, refer to Table 1 of Chapter Critical Care Scoring)

Hepatic failure (presence of both of the following)—
- Serum bilirubin >6 mg%
- Prothrombin time >4 sec over control (in absence of systemic anticoagulation)

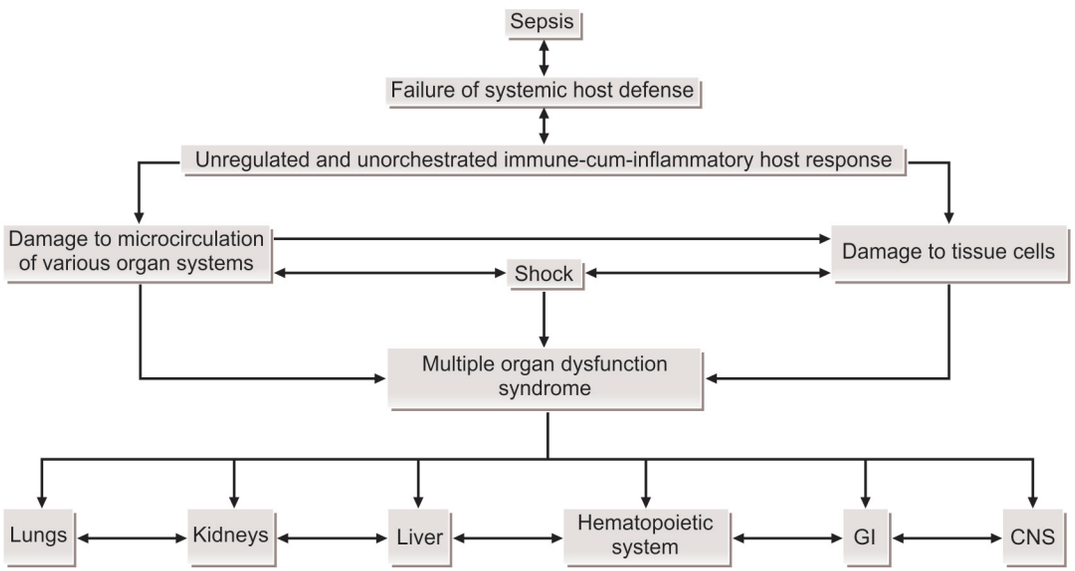
*If the patient had one or more of the following during a 24-hr period (regardless of other values), organ system failure (OSF) existed on that day.
†Excluding patients on chronic dialysis prior to hospital admission.
Source: Modified from Matuschak GM. Multiple system organ failure. In: Hall JB, Schmidt GA, Wood LDH (Eds). Principles of Critical Care. New York: McGraw-Hill Inc.; 1992. pp. 613-36.

Table 1: Sequential Organ Failure Assessment (SOFA) Score

	0	*1*	*2*	*3*	*4*
Respiration— - PaO_2/FiO_2	>400	≤400	≤300	≤200 with ventilatory support	≤100 with ventilatory support
Coagulation— - Platelets (x $10^3/mm^3$)	>150	≤150	≤100	≤50	≤20
Liver—Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular— - Hypotension	No hypotension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any dose)*	Dopamine >5 or epi ≤0.1 or norepi ≤0.1*	Dopamine >15 or epi >0.1 or norepi >0.1*
Central nervous system— - Glasgow coma score	15	13–14	10–12	6–9	<6
Renal— - Creatinine (mg/dL) - Urine output	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500 mL/day	>5 or <200 mL/day

*Adrenergic agents administered for at least 1 hour (doses given are in µg/kg per minute).
Abbreviations: epi, epinephrine; norepi, norepinephrine.

Flowchart 1: Inter-relationships between organ systems in the evolution of the multiple organ dysfunction syndrome (MODS)



of oliguria and azotemia to reflect renal dysfunction and failure, just as one would accept a Glasgow coma score of less than 6 to denote severe dysfunction involving the neurological system. But what constitutes dysfunction of the gastrointestinal system? How does one quantitate degree of dysfunction in this system? There is no measurement today that reflects a breakdown of the mucosal barrier of the gut, permitting intraluminal bacteria and their products access to the portal and systemic circulations. Similarly, hepatobiliary dysfunction and poor protein synthesis by the liver may not reflect and may well be dissociated from the phagocytic function of Kupffer cells, or production by the liver cells of inflammatory peptide and lipid mediators that produce far-ranging effects in distant organ systems. We are thus abysmally ignorant of measurement of functions that may well play a crucial role in amplifying disturbed function in various organ systems.

4. Disturbed function in each organ system may not have equal pathogenetic significance in the evolution of the syndrome. If this be so, the view that the clinical expression of multiple organ dysfunction and its outcome merely depend on the numerical sum of specific organ failures, is simplistic and may not be true. The interdependency and interrelationship of organ systems, and the special importance of factors (related to organ dysfunction) which worsen host defense failure and further impair regulation of immune and inflammatory responses by the host, are crucial to the concept and evolution of the syndrome (Flowchart 1).

ETIOLOGY

Numerous reports and our own experience over many years confirm that sepsis is the main predisposing cause of multiple organ dysfunction.[11,12] However, many causes other than sepsis and septic shock can also result in this syndrome. Trauma and shock from causes other than sepsis are classic examples in which the clinical features of multiple organ dysfunction may exist without any evidence of infection.

The ACCP or SCCM Consensus Conference in our opinion has given a valuable semantic classification of the terminology related to sepsis. The reader is referred to their description which is detailed in the Chapter Sepsis and Septic Shock.

In a tropical setting, the etiology of multiple organ dysfunction is best classified thus.

Sepsis

Sepsis by definition is an expression of the systemic inflammatory response syndrome (SIRS) (see Chapter Sepsis and Septic Shock) due to infection. The commonest infection producing sepsis is a bacterial one, and the commonest sites of bacterial infection producing sepsis and related multiple organ dysfunction in our ICU are bloodstream infections, intra-abdominal sepsis, pulmonary infections and urosepsis. However, localized infection in the form of an abscess anywhere in the body, as also nosocomial infections, if undetected and untreated, result in sepsis which may evolve into multiple organ failure. Gram-positive and Gram-negative aerobic or anaerobic organisms can produce localized or generalized sepsis, and culminate in multiple organ dysfunction.

Tropical Infections[13]

For tropical infections, see Chapter Community-Acquired Pneumonias Requiring Critical Care. These are of special importance in our part of the world—

- The most important tropical problem responsible for multiple organ dysfunction and failure is severe infection due to *Plasmodium falciparum*.[14]
- Extensive miliary tuberculosis and disseminated hematogenous tuberculosis, particularly in immunocompromised individuals (as those on corticosteroids or other immunosuppressant drugs), can lead to a rapidly evolving multiple organ failure. The diagnosis may be missed if not suspected. The patient is generally too ill to provide sputum for examination.
- Tetanus is another important cause. Multiple organ failure is most often due to iatrogenic sepsis, but it could also result directly from the disease *per se*.
- Fulminant typhoid and salmonella infections can occur anywhere in the world, but are commoner in poor developing countries. They can result in a picture of sepsis and multiple organ dysfunction.

  A peculiar though uncommon form of Gram-negative infection following the ingestion of contaminated food is also occasionally observed in the tropics. This results after a very brief period of gastrointestinal symptoms, to features of sepsis, culminating in acute lung injury. Liver cell dysfunction and renal dysfunction also often occur. Blood cultures if done early may grow *E. coli* or *Klebsiella*. Early treatment and good critical care generally lead to recovery.
- Fulminant amebic infections characterized by an amebic abscess of the liver rupturing into the peritoneum and/or the lung or the pleural space, or necrotizing amebic colitis can also cause multiple organ dysfunction.

Fungal, Viral, Leptospiral and Rickettsial Infections

These infections can produce the picture of sepsis with multiple organ failure. Fungal infections are assuming increasing importance. They should be particularly kept in mind in immunocompromised patients, neutropenic patients, in patients who have received antibiotic therapy and in those on intravenous hyperalimentation.

Fulminant dengue can lead to multiple organ dysfunction through hemorrhagic shock or through transudation of fluid in various organ systems, or through bleeding into various organ systems. Hemorrhagic viral fevers, like the Ebola virus or the Hanta virus fevers, are fortunately confined to specific areas in Africa. They are fulminant and frequently fatal. MODS and death result from bleeding and widespread cell necrosis in various organ systems of the body.

Multiple organ dysfunction syndrome in rabies is of academic interest, as patients die within 24–72 hours. One patient, who was offered intensive care in our unit, survived for 26 days and then succumbed. MODS was observed in this patient.[15]

Severe leptospiral infections can cause hepatic, renal and CNS dysfunctions. Respiratory failure may be due to ARDS or to alveolar hemorrhage.

Severe Hemorrhage Causing Shock or Shock from Any Cause

Each of the above entities can lead to multiple organ dysfunction.

Trauma

Trauma is an extremely important cause of multiple organ dysfunction, perhaps second only to sepsis. In hospitals with trauma units, it constitutes the most important cause of MODS. Trauma can cause multiple organ dysfunction and failure, even in the absence of any evidence of infection. When infection does complicate trauma, it adds to the risk of multiple organ dysfunction.

Other Conditions Not Initiated by or Due to Infection

a. Important conditions—
   - Burns.
   - Acute pancreatitis.
   - Multiple blood transfusions.

Table 2: Incidence and mortality of multiple systems organ failure

				Mortality rate per No. of organ system failed		
Study	*Patients*	*ICU population*	*Incidence (%)*	*1*	*2*	*3*
Knaus et al.[6]	5,815	M, S[2]	819 (15)	40	60	100
ECMO[a]	490	M, S[3]	74 (15.1)	40[1]	55	80–100
Fry et al.[5]	553	S[4]	38 (6.9)	30[1]	60	85–100
Montgomery et al.[b]	207	M, S[3]	22 (10.6)	NE	NE	NE
Pine et al.[c]	106	S[5]	21 (19.8)	10	50	100
Bell et al.[d]	84	M, S[3]	40 (47.6)	40	54	80–100

[1] Multiple systems organ failure (MSOF) defined as severe acquired dysfunction in ≥2 organ systems during critical illness or after trauma or major operation.
[2] Random ICU admissions prospectively followed.
[3] Patients at risk for ARDS or with established ARDS prospectively identified.
[4] Emergency surgical patients retrospectively reviewed.
[5] Patients with trauma or intra-abdominal sepsis retrospectively reviewed.
[6] Patients with pre-existing intra-abdominal sepsis prospectively followed.

Abbreviations: M, medical patients; S, surgical patients; NE, not evaluable.
Source:
[a] National Heart, Lung and Blood Institute, Division of Lung Diseases (1979), Extracorporeal support for respiratory insufficiency: a collaborative study. NIH, Bethesda, MD.
[b] Montgomery AB, Stager MA, Carrico CJ, et al. Causes of mortality in patients with adult respiratory distress syndrome. Am Rev Respir Dis. 1985;132:485-9.
[c] Pine RW, Wertz MJ, Lennard ES, et al. Determinants of organ malfunction or death in patients with intra-abdominal sepsis. Arch Surg. 1983;118:242-9.
[d] Bell RC, Coalson JL, Smith JD, et al. Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med. 1983;99:293-8

- Poisonings, in particular organophosphorus poisoning.
- Following complications during cardiopulmonary bypass surgery.
- Eclampsia.
- Severe vasculitides.
- Acute connective tissue disease.

b. Less common conditions—
- Thrombotic thrombocytopenic purpura.
- Atrial myxoma.
- Cholesterol emboli syndrome.
- Steven-Johnson syndrome, toxic epidermal necrolysis.
- Hemophagocytic syndrome.

It is extremely important to rule out noninfectious causes of MODS, particularly in patients diagnosed as sepsis, whose blood cultures are negative and whose source of sepsis is undetermined. In our experience, MODS caused by unusual poisonings, acute vasculitides (particularly acute Wegner's granulomatosis), acute connective tissue disease, atrial myxoma, thrombotic thrombocytopenic purpura, though rare, can be easily missed and wrongly diagnosed as sepsis with MODS.

Severe Derangement in the Function of Any One Major Organ System

Severe dysfunction of one organ system can over a period of time lead to dysfunction of multiple organ systems. A classic example is acute liver cell failure, irrespective of its etiology (e.g. drugs, poisons, viral causes). In a short span of time, multiple organ dysfunction is observed. Similarly, persistent or prolonged severe cardiac dysfunction, or acute renal failure can result in MODS. Again, trauma to the lungs with massive contusions produces a primary respiratory failure. Over a period of time, other organ systems can be secondarily involved.

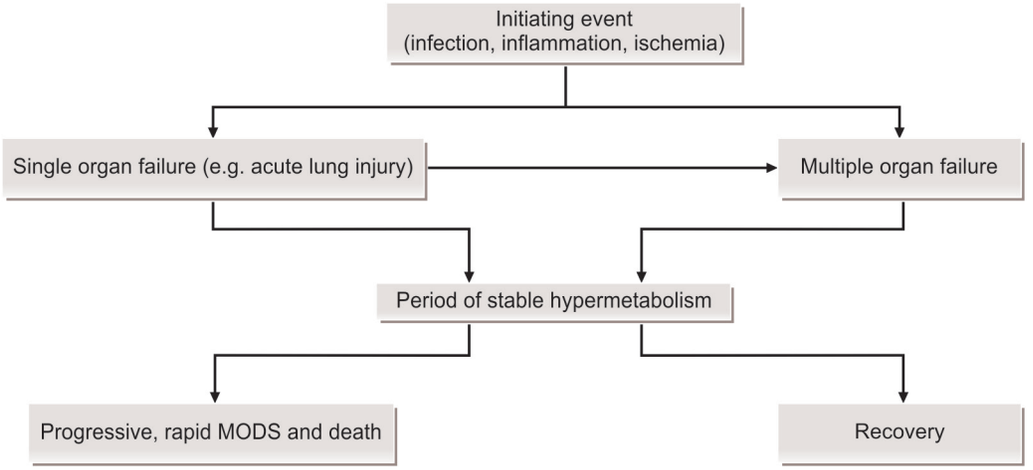
EPIDEMIOLOGY

As mentioned earlier, the incidence of MODS continues to show a steady rise. A busy, efficient, ICU which is equipped with good life-support systems and is engaged in looking after critically ill patients will have a high incidence of MODS. The incidence and mortality rate in the West is illustrated in Table 2. If MSOF is defined as severe acquired dysfunction in at least two organ systems lasting for at least 24–48 hours during the course of a critical illness, infection or injury, then MSOF complicates 7–15% of all ICU admissions in the West.[5,9] We have noted that approximately 10% of all the admissions in our ICU develop MSOF.

NATURAL HISTORY AND CLINICAL FEATURES

Sepsis, severe trauma or ischemia to tissues, shock from any cause and severe inflammation as in acute pancreatitis are important causes of multiple organ dysfunction and failure. In these conditions, the natural history of MODS in an ICU setting may evolve through the following four phases—(1) shock, (2) resuscitation, (3) a hypermetabolic phase and finally (4) the clinical evolution of multiple organ dysfunction, which culminates either in death or recovery. This need not however always be so. Polytrauma, sepsis, ischemia to a limb and even pancreatitis can result from the very start in the SIRS, progressing to a slow or quickly evolving multiple

Flowchart 2: Natural history of multiple organ dysfunction syndrome (MODS)



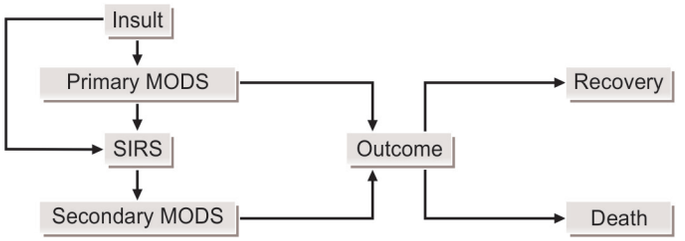
organ dysfunction without causing shock to start with. If shock does however occur as the first phase, resuscitation is generally achieved in a number of patients, provided that infection or any other etiological factor is controlled and the patients are adequately supported during this phase. In a small group of resuscitated patients the illness next enters a hypermetabolic phase. The natural history of MODS is illustrated in Flowchart 2.

The clinical features of the hypermetabolic phase include all the features of the SIRS—fever, leukocytosis, tachycardia and tachypnea.[6] In fact, the seeds of multiple organ dysfunction are sown during this stage, or probably even earlier. The hypermetabolic state that characterizes the SIRS may be associated with obvious evidence of a single organ dysfunction (typically the lung or kidney) or very subtle clinical or laboratory findings of early dysfunction of more than one organ system. Recovery can still ensue though the mortality with well-marked single organ dysfunction is around 10%.

The final stage of multiple organ dysfunction is characterized by sequential or at times, well-nigh concomitant failure of other organ systems. It is almost certain that at least in acute infections and sepsis there is global cellular injury; however, different organ systems manifest overt or clinical features of dysfunction at differing times. More often than not, the lung shows the first manifestation of dysfunction. Whether this is due to a special vulnerability of this organ system, or whether this early involvement is more apparent than real, is undecided. Lung dysfunction related to disturbed gas exchange is easily detected both on clinical grounds, and on standard laboratory measurements.

The tempo of the natural history is dependent both on the etiology and the host response to insult or injury. Multiple organ system dysfunction in our experience can evolve quickly, and kill the patient within a week despite the best of care and support. At other times, sequential organ failure is observed, and the natural history may extend from 2 to 6 weeks before death or recovery ensues.

Flowchart 3: Outcome of primary and secondary multiple organ dysfunction syndrome (MODS)



The ACCP or SCCM Consensus Conference[6] suggested that MODS develops by two relatively distinct, but not mutually exclusive pathways. Primary MODS is due to direct injury or insult to an organ system. Organ dysfunction occurs early, and is directly due to this insult. Examples of primary MODS due to a direct injury or insult to one organ system include pulmonary injury following inhalation of noxious fumes, or following contusion of the lungs as a result of trauma, coagulopathy induced by multiple blood transfusions and acute renal shutdown due to drugs. In primary MODS, the role of an abnormal and excessive host inflammatory response, both at the onset and during progression of the syndrome, is not so evident as in secondary MODS (Flowchart 3).

Secondary MODS is due to an indirect injury to one or more organ systems. It is in fact a consequence of the host response, which results in an immunoinflammatory response in organs distant from the site of the initial insult. Secondary MODS is observed in acute infections, sepsis, shock and trauma or ischemia to tissues.

Risk factors in the development of MODS have been arrived at from a study of 5,815 randomly selected ICU admissions from 13 United States medical centers, using the APACHE II scoring system.[8,9] The major risk factors for the development of this syndrome are: (i) severity of disease; (ii) presence of sepsis or infection at the time of ICU admission; (iii) age greater than 65 years.

Box 2: Clinical risk factors for the development of MODS

- Severity of disease (grading according to APACHE II score)
- Presence of sepsis or infection at the time of admission
- Age >65 years
- Severe, persistent shock of any etiology
- Major, prolonged surgery, trauma, presence of devitalized tissue
- Severe burns
- Persistent hypotension (>24 hours) after admission
- Persistent liver or renal dysfunction
- Uncontrolled diabetes
- Immunocompromised patients
- Malnutrition

Table 3: Stage I of MODS

General appearance	Normal or mildly restless
Cardiovascular function	Increased volume requirements
Respiratory function	Mild respiratory alkalosis
Renal function	Oliguria, limited diuretic responsiveness
GI function	Distension
Hepatic function	Normal or mild cholestasis
Metabolism	Hyperglycemia, insulin requirement
CNS	Confusion
Hematology	Variable

Source: Reference 16.

Table 4: Stage II of MODS

General appearance	Ill appearing, restless
Cardiovascular function	Hyperdynamic, volume-dependent
Respiratory function	Tachypnea, hypocapnia, hypoxemia
Renal function	Fixed output, minimal azotemia
GI function	Intolerance to enteral feeding
Hepatic function	Hyperbilirubinemia, prolonged PT
Metabolism	Severe catabolism
CNS	Lethargy
Hematology	Thrombocytopenia, leukopenia, leukocytosis

Source: Reference 16.

Table 5: Stage III of MODS

General appearance	Obviously unstable
Cardiovascular function	Shock decreased cardiac output, edema
Respiratory function	Severe hypoxemia, ARDS
Renal function	Azotemia, indication for dialysis
GI function	Ileus, stress ulceration
Hepatic function	Clinical jaundice
Metabolism	Metabolic acidosis, hyperglycemia
CNS	Stuporous
Hematology	Coagulopathy

Source: Reference 16.

Other major risk factors observed in our unit include severe, persistent shock from any cause, persistent hypotension, prolonged major surgery, trauma, burns, pre-existing chronic disease of a major organ system, in particular liver cell dysfunction, immunocompromised patients, and a background of poor nutrition. These factors have been listed in Box 2.

The clinical recognition of multiple organ dysfunction is easy to the trained eye. An important feature in the diagnosis of early dysfunction is the recognition of background factors known to cause the development and evolution of this syndrome.

Carrico and colleagues[16] have tabled a brief clinical description of increasing severity of multiple organ dysfunction (Tables 3 to 6). The greatest flaw in this tabulated description of Stages I, II and even III of MODS is the assumption that each organ system fails at the same pace and at the same time. This presumption is an exception rather than the rule. In clinical practice just two organ systems may show severe or Stage III changes, with barely any involvement of other organ systems for many days—at times right up to the time of death. Yet, in some instances, concomitant or a quickly sequential failure of one organ system after another may be observed.

Table 6: Stage IV of MODS

General appearance	Moribund
Cardiovascular function	Vasopressor dependent, edema, rising $S\dot{v}O_2$
Respiratory function	Hypercapnia, barotrauma
Renal function	Oligo-anuria, instability on dialysis
GI function	Diarrhea, ischemic colitis
Hepatic function	Transaminase elevations, deepening jaundice
Metabolism	Muscular wasting, lactic acidosis
CNS	Coma
Hematology	Uncorrectable coagulopathy

Source: Reference 16.

PATHOPHYSIOLOGY[17]

(See Chapter Sepsis and Septic Shock)

Multiple organ dysfunction syndrome can be considered to result from a combination of impaired host defenses, and inappropriate, uncontrolled host regulation of immunoinflammatory, vascular, neural, metabolic, endocrine responses, which have far-reaching deleterious effects

on the organ systems of the body. The body response to injury whether related to sepsis or non-infectious causes is remarkably similar. Also the type of organisms causing infection (e.g. Gram-negative bacilli, Gram-positive cocci, viruses, protozoa or fungi) does not make any difference to the final expression of the syndrome. Unfortunately the vicious downward spiral of worsening organ function culminating in death is not always necessarily arrested by identifying and treating the etiological factor responsible for the syndrome.

The initiating cause of SIRS and MODS can induce—

- Direct injury to cells.
- Indirect injury through activation of serum factors.
- Indirect injury due to cellular activation.
- Endothelial injury and dysfunction, which worsens inflammation and induces coagulation.
- Tissue hypoxia.
- Apoptosis.

Direct Injury to Cells

This is illustrated in sepsis when the lipopolysaccharide fraction of the endotoxin of Gram-negative organisms during the period of endotoxemia can directly damage endothelial capillary cells in different organs, and perhaps even directly impair tissue cell function.

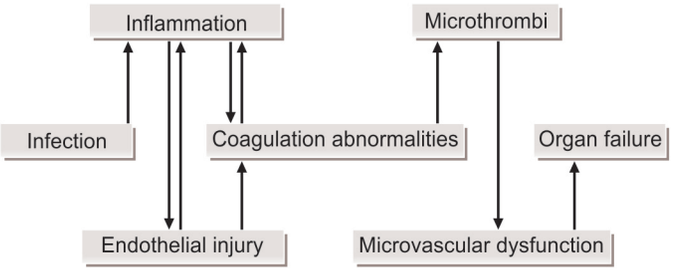
Activation of Serum Factors

Activation of complement can result not only from the effects of endotoxin in sepsis, but also from other diverse initiating factors, viz. trauma, ischemia or poor generalized tissue perfusion as in shock. Complement kinin-kallikrein coagulation and fibrinolysis cascades can lead to widespread tissue injury. Complement activated neutrophil mediated injury is also important in the genesis of organ dysfunction.

Cellular Activation[18]

Platelets, polymorphonuclear leukocytes and macrophages when activated can produce and release different mediators, which, if uncontrolled, can induce and amplify damage to cells in various organ systems of the body. Great attention has been focused on the role of activated mononuclear cells and on the activated macrophage system, both in the SIRS, and in the MODS. More than thirty different mediators, produced and released endogenously have been identified. These can have local and systemic actions. The role of cytokines in the regulation of the inflammatory response of the body to "injury" is of proven importance. The term "cytokine" refers to cell derived peptide molecules which cause a target cell to alter its functional activities. The tumor necrosis factor (TNF), interleukin-1 and interleukin-6 are cytokines credited with an important proinflammatory role in SIRS and MODS. Platelet-activating factor, products of arachidonate metabolism and, in particular, metabolites produced through the cyclo-oxygenase pathway have important effects on the vasculature, and on other mediators. It is just not the effect of individual mediators

Flowchart 4: Physiopathology of sepsis



that matters, but the interaction and inter-relation between them that is important. The polymorphonuclear cell, though a crucial factor in the defense against bacterial invasion, can also play an important role in mediating cell injury. Neutrophils can cause injury to other cells by the release of reactive metabolites to oxygen (superoxides, oxidants), and the release of proteolytic enzymes during degranulation.

Endothelial Injury

The role and metabolic activity of the endothelium is also of great importance in the development of SIRS and MODS. Injury to the endothelium can be direct as in endotoxemia or indirect as in shock. Endothelial injury promotes coagulation and reduces fibrinolysis that ordinarily counters the tendency to coagulation. Previously, inflammation caused by release of cytokines and proinflammatory mediators was considered the dominant feature in the cascade of events that led to MODS. The current concept is that inflammation, coagulation and fibronolytic abnormalities act together in the disease process. Investigations into the time course and extent of coagulation and fibrinolytic abnormalities in severe sepsis and their relation to endothelial dysfunction have pointed to the crucial role of an imbalance in hemostatic mechanisms. This imbalance results in a coagulopathy and microvascular thrombosis, which may well be a vital driving force in the evolution of progressive multiple organ dysfunction and death (Flowchart 4).

Tissue Hypoxia

Tissue hypoxia can lead to injury and even death of cells in multiple organ systems and is an important cause of MODS. A major casualty of severe sepsis is the cardiovascular system. There is cardiovascular dysfunction (both systolic and diastolic), systemic vascular changes, regional vascular dysregulation and microcirculatory damage and dysfunction. Regional maldistribution in blood flow and microcirculatory dysfunction and failure may be impossible to detect and may continue to progress if the underlying cause (e.g. sepsis) is not successfully treated. The end result is tissue hypoxia even when hemodynamic parameters with regard to the overall systemic circulation have been restored through fluid resuscitation and vasopressors. Adequate oxygen delivery by measures that ensure a central venous oxygen saturation of 70% results in a significant reduction in mortality.

Tissue hypoxia can also result from impaired mitochondrial oxygen utilization by the cells due to a direct effect on cell function by noxious agents or secondary to microcirculatory dysfunction. Both tissue hypoxia and impaired utilization of oxygen due to mitochondrial dysfunction lead to raised lactate levels.[19] Impaired utilization of oxygen by tissue cells ultimately leads to a rise in the central venous oxygen saturation.

Apoptosis

Apoptosis is programmed cell death. A pathological activation of programmed cell death appears to be a feature of MODS. Apoptosis is induced by an extrinsic (receptor dependent) or intrinsic (receptor independent pathway). The extrinsic pathway is activated by Fas receptor (CD 95) or the TNF receptor. The receptors of the extrinsic pathway activate procaspase 8 to active caspase 8, which in turn activates caspase 3 which is ultimately responsible for apoptosis. The intrinsic pathway is induced by DNA damage, the mitochondrial membrane potential being then altered by the signal protein p53, which mediates the activation of caspase 9. Active caspase 9 activates caspase 3 which again is the final step that leads to cell death.

In conclusion, the pathogenetic mechanisms responsible for diffuse cellular injury and MODS are as yet poorly understood. The host responses to infection or injury that lead to MODS are dynamic, variable, interconnected and according to a current concept, perhaps non-linear in nature.[20] If this be so, an analytical approach may fail to evaluate the emergent properties of this network or system. This may well explain the lack of response to various anti-mediator therapies observed in numerous clinical trials. *It appears that organs talk to each other and that cells within them do likewise at the molecular level. It is this communication system which probably adjusts the balance between health and disease*. We need to decipher this communication system, if we are to find means to arrest the downward spiral frequently observed in severe MODS.

Role of the Gut and Liver in MODS

What causes an ongoing stimulation of mediator response? This continues to exercise the minds of many researchers in this field. Attention is being increasingly focused on the gastrointestinal tract as a source that fuels the inflammatory response. The gut is an effective barrier which prevents bacillary organisms and their products from entering the systemic circulation and injuring the host. It is suggested that in shock, trauma, burns or sepsis, changes occur in this protective barrier, resulting in a bacterial translocation. This allows a continuous uncontrolled release of bacteria, antigens and endotoxin into the lymphatics and the circulation, to which the body responds by the stimulation and release of inflammatory mediators. The liver may ordinarily detoxify or destroy these products if the Kupffer cell function is adequate.[21] These Kupffer cells represent 70% of the fixed macrophage population of the body, and in addition influence hepatocyte functions such as protein synthesis. Ischemia to the gut from any cause also depresses the immunological function of the gut, further enhancing the activity of the bacterial flora within it. Factors predisposing to bacterial translocation are given in Box 3. The sequence of events in gut-liver axis leading to sepsis is illustrated in Figure 1.

Box 3: Factors predisposing to bacterial translocation

- Change in normal flora
- Impaired cell-mediated immunity
- Severe malnutrition
- Severe shock
- Total parenteral nutrition
- Sepsis—mainly intra-abdominal sepsis
- Severe burns
- Intestinal obstruction

The crucial role of the liver in the pathogenesis of MODS is evident in the above situation. A poorly functioning liver due to current or pre-existing liver disease, or a liver whose Kupffer cells are unable to cope with the load of bacteria or their products caused by translocation, can lead to an overwhelming invasion of the systemic circulation by bacteria and their products. These wreak havoc by their direct effect on endothelial cells and tissue cells, or act indirectly through stimulation of inflammatory mediators. Mechanisms that impair hepatocellular function in MODS are detailed in Box 4.

Metabolic Dysregulation in the SIRS[22]

Metabolism is controlled to a significant extent by inflammatory mediators, and is less responsive to the normal regulatory mechanisms within the body. As a consequence there is—

- A rise in energy demands manifested by increase in oxygen consumption, and an increased production of carbon dioxide with metabolic acidosis.
- Increase in gluconeogenesis and lipolysis.
- Energy production by the process of aerobic glycolysis.
- A severe catabolic state characterized by a loss in lean body mass that does not respond to exogenous aminoacid or protein administration. There is also a redistribution of the body nitrogen to the areas of active protein synthesis, e.g. viscera or wounds.[23]

SIRS and MODS are in continuum, and the transition from SIRS to MODS is often characterized by the following features—

- Worsening liver function, possibly affected by activated Kupffer cells.[21]
- Impairment of extraction and utilization of oxygen at the microcirculatory level, which could be related to capillary damage or to disturbed cellular function at the tissue level. Hypoxia to tissue cells leads to progressive worsening of organ function.
- The clinical expression of the above feature is an increase in the mixed venous oxygen saturation ($S\dot{v}O_2$) together with an increase in blood lactic acid levels.

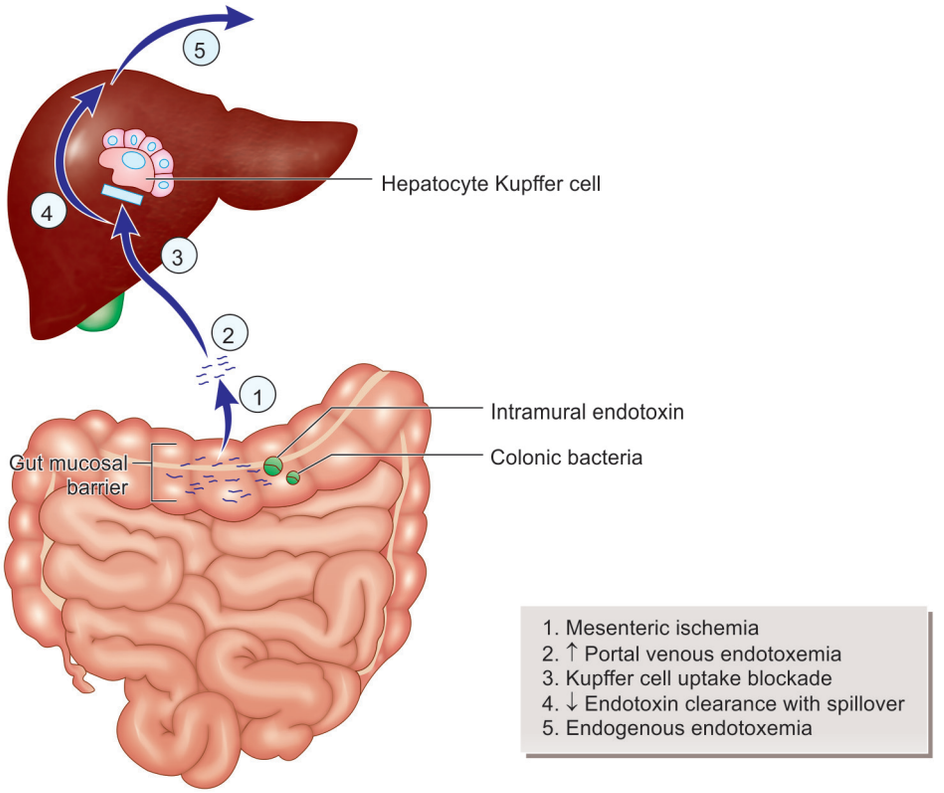


Fig. 1: Sequence of events in gut-liver axis leading to septicemia

Source: Modified from Matuschak GM. Multiple system organ failure. In: Hall JB, Schmidt GA, Wood LDH (Eds). Principles of Critical Care. New York: McGraw-Hill Inc.; 1992. pp. 613-36.

Box 4: Factors which impair hepatocellular function in MODS

- Significant pre-existing liver cell disease
- Bacterial translocation
- Mesenteric/hepatic ischemia

PROGNOSIS

The greater the number of organ failure and longer the duration, the greater is the mortality (Table 2).[5,9] Knaus and colleagues[8,9] from a study of their large database, and using the APACHE II scoring system, noted that any single organ system failure lasting for more than 1 day, resulted in an inhospital mortality of approximately 40%; persistent failure in two organs over the same period led to a 60% mortality; failure of any three systems led to a mortality approaching 100%. This study also supported the view that a predisposition to MODS, and mortality due to MODS, increased with age (>65 years). The APACHE III system is an even more recently designed scoring system to objectively assess risk for mortality in critically ill hospitalized patients[24] (see Section I). It is a complicated system using seventeen physiological variables, and its utility vis-à-vis clinical judgment based on experience needs to be proved. With improved critical care and better support to all organ system, the current mortality is much less than that reported by Krauss et al. The current mortality rate increased with increasing number of organ dysfunctions as follows: no organ dysfunctions (10% mortality), 1 organ dysfunction (10–15% mortality), 2 organ dysfunction (20–25% mortality), 3 organ dysfunction (30–35% mortality).[25] *However, failure of more than three organs even today is reported in the West to have a mortality of close to greater than 80%.*

There are some important reservations that need to be discussed in relation to even current mortality figures reported from the West—

a. The outcome of the scoring system in predicting mortality in individual patients admitted to the ICU can be misleading. The scoring system may be wrongly computed and marked, leading to a nihilistic approach to potentially salvageable patients. Both the APACHE II and the Mortality Prediction Models (MPM) developed by Teres et al.[26] have a misclassification rate as high as 15%.
b. The dismal outcome predicted holds true for the advanced stage of MODS—i.e. when organ dysfunction and the natural history of the disease are very severe or well beyond the point of return.
c. Mortality figures with lesser degrees of multiple organ dysfunction, as judged for example by the use of SOFA scores, are not as dismal as those quoted above.

d. The mortality figures reported in severe multiple organ dysfunction occurring in the West do not necessarily apply to multiple organ dysfunction and failure occurring in tropical problems.[8,9] A severe degree of multiple organ dysfunction often involving three or more organ systems is thus often present in *P. falciparum* infections. The organ systems frequently involved are the CNS, the kidneys, the hematopoietic system, the lungs and the liver. The mortality with severe dysfunction, in our experience, is about 33% even when more than three organs are involved for over a week. In a similar fashion, in our experience, mortality in severe tetanus with multiple organ failure does not exceed 29%. Mortality in multiple organ failure in disseminated hematogenous tuberculosis lasting for many days is about 50%. Our last 4 patients with disseminated hematogenous tuberculosis and multiple organ failure, all survived; one patient had evidence of more than four organ system dysfunctions for over 3 weeks, and yet recovered. All our patients with severe typhoid infection causing sepsis and multiple organ failure recovered; all our patients with severe Gram-negative infection and multiple organ failure following ingestion of contaminated food, also recovered. Fulminant amebic infections and necrotizing amebic colitis causing multiple organ failure have a comparatively bad prognosis with a mortality rate of 50%.
e. In our rather small series of 50 patients with different fulminant tropical problems causing MODS, a SOFA score of 16 was associated with a 50% mortality. In contrast, a study by Vincent and colleagues, in which 74% of the patients with four organ failure had bacterial infection, a SOFA score of 16 was associated with greater than 80% mortality.[10] The improved mortality in MODS due to tropical problems could be related to prompt good critical care soon after the onset of symptoms, and the availability of specific therapy for many tropical problems—artesunate and quinine for malaria, a proven effective management protocol for severe tetanus, anti-TB drugs for disseminated hematogenous tuberculosis, ceftriaxone for typhoid, and specific drugs for amebic and leptospiral infections. However, the present impression that MODS due to tropical infections causes a lesser mortality compared to bacterial infections needs to be confirmed by a larger prospective study.
f. Any scoring system used for predicting prognosis is arbitrary. A scoring system must be stringent, but must also take into consideration milder or more moderate forms of MODS. A larger base of exact variables, and of various combinations of variables of organ dysfunction in relation to outcome, merits further study to predict a more realistic prognosis of MODS.
g. A nihilistic approach to severe MODS is against the basic tenet of critical care medicine. Many an individual patient has defied perfectly derived statistical figures, so that he or she survives when clearly expected to die.

MANAGEMENT

The treatment of MODS is unsatisfactory. There are three reasons for this—

1. The cause or underlying etiology responsible for initiating MODS very frequently cannot be eradicated. This is particularly so in patients with abdominal sepsis related to multiple perforations, which cannot be permanently tackled due to technical reasons. Unless the peritoneal leak from a diseased section of the bowel is permanently sealed, no treatment is of avail. The better the support and care offered to such unfortunate patients, the more protracted the agony prior to death. Another example is abdominal sepsis related to acute suppurative pancreatitis. Despite the best surgical techniques available, it may be impossible to totally eradicate all sources of infection in a critically ill individual.
2. When the cause of SIRS and MODS can be successfully treated, the chances of recovery significantly improve. Even so, a number of patients progress to worsening multiple organ dysfunction, and ultimately die.
3. Beyond a certain stage in the natural history of MODS, there is a point of no return, perhaps because the underlying mechanisms responsible for organ injury are self-perpetuating. Currently, we have no means to arrest this downward trend leading to death. This perhaps explains why successful treatment of the cause responsible for initiating the pathophysiological cascade does not necessarily lead to recovery.

The importance of possible prevention of this syndrome is thus self-evident.

PREVENTION

Only a few basic principles are outlined in this chapter. Perhaps the most important preventive measure is the rapid, appropriate resuscitation of shock, whatever its etiology. Since MODS is common in surgical patients, it is wise to optimize organ function before major surgical procedures, as this decreases the incidence of both perioperative and postoperative complications.[27] Accurate monitoring and maintenance of organ function during surgery, and above all good surgical technique in poor risk patients, go a long way in prevention of disastrous postoperative sequelae. The importance of appropriate management of early pulmonary dysfunction, so that ventilation-perfusion inequalities stand corrected, and adequate arterial oxygen saturation is maintained or restored, is being increasingly realized. One should never hesitate to offer ventilator support to achieve this objective.

Management protocols designed to support or treat one organ system should not result in possible dysfunction of some other organ system.

Selective gut decontamination using a combination of oral antibiotics (e.g. tobramycin, polymyxin, nystatin or amphotericin) continues to be used in many critical care units as a means of sterilizing the bowel and reducing the risk of nosocomial pneumonias, and translocation of bacteria

from the gut. Though a few prospective studies have shown a decreased risk for nosocomial infections, there has been no improvement in either the incidence or overall mortality of MODS.[28] Though Rocha and colleagues[29] showed fewer nosocomial infections, there was an increase in resistant bacterial isolates from the treated group, and there was no improvement in the cost-benefit ratio.

TREATMENT

The treatment of evolved MODS is basically supportive; the following five features need to be emphasized—

1. Eradication or at least control of the etiology responsible for the syndrome.
2. Maintenance of optimal oxygen transport to the tissues.
3. Metabolic support.
4. Support to organ systems viewed from an overall perspective.
5. Notwithstanding the grim prognosis forecast for patients with three or more organ failures lasting for 3 days or more, according to the APACHE II scores,[8,9] a nihilistic attitude to these patients is unjustified and ethically wrong.

Eradication or Control of Underlying Etiology

Recovery is impossible if the source or origin of this syndrome remains uncontrolled in a patient. An abscess must thus be drained however ill the patient or the source of acute peritonitis must be removed insofar as this is possible, or a full thickness burn excision with skin grafting must be undertaken in spite of the patient being critically ill.

Maintenance of Oxygen Transport

[See Chapter Sepsis and Septic Shock and Chapter Acute Lung Injury and Acute Respiratory Distress Syndrome (ARDS)]. In severe MODS due to sepsis, oxygen consumption may be reduced in spite of adequate oxygen delivery, suggesting an inability of the tissues to utilize oxygen. The resuscitation of shock should therefore take into paramount consideration the maintenance of optimal oxygen transport. As mentioned in earlier chapters, increase in oxygen transport involves maximizing oxygen content and cardiac output. Oxygen content is increased by: (a) maintaining a high arterial PaO_2 (preferably ≥70 mm Hg), and an oxygen saturation of over 90% and (b) maintaining the hemoglobin at 10 g/dL. Cardiac output is optimized by taking into consideration the preload, contractility, and afterload, and by treating disturbances in rate and rhythm which may adversely affect the cardiac output. The concept of achieving a supramaximal delivery of oxygen by increasing cardiac output (through the use of inotropes) to supramaximal levels is no longer valid and can perhaps do more harm than good (see Chapter Overview of Shock Syndromes).

Metabolic Support

Patients with MODS suffer tremendous weight loss and lose a great deal of lean muscle mass during the course of their illness. This problem is indeed more acute when the syndrome evolves against a background of poor nutrition or malnutrition, as is often the case in third world countries. Our experience with MODS in tropical countries has convinced us that nutritional support reduces both morbidity and mortality. This is perfectly illustrated in the management of fulminant tetanus in patients from a poor strata of society with poor nutritional status.[30]

The principles of nutritional support in patients with SIRS and MODS are to some extent being revised. Current concepts are briefly enunciated below—

a. The objective in these hypermetabolic, hypercatabolic patients is to attain nitrogen equilibrium using nutritional formulae that offer the maximum benefit with the least morbidity.[31] It is now believed that too many calories and the wrong combination of caloric substrates can do more harm than good.[31]
b. It is not necessary to use excessive daily total caloric intakes—the recommendations vary greatly. We use 30 calories/kg bodyweight with not more than 5 g/kg per day as glucose or carbohydrates. Excessive carbohydrate intake should be avoided because of the higher risks of hepatic lipogenesis and excessive carbon dioxide production.
c. Fat emulsions (n-6 polyunsaturated fatty acids) are restricted to 0.5–1 g/kg per day. The use of larger quantities of fat emulsions chiefly consisting of n-6 long-chain polyunsaturated fatty acid triglycerides can lead to cholestasis, hypoxemia, bacteremia and immune suppression.[32]

   Arachidonic acid is an omega-6 polyunsaturated fatty acid which is produced from linoleic acid and is commonly found in soybean oil and safflower oil emulsions. Products of arachidonic acid metabolism include prostaglandins and leukotrienes. A few leukotrienes produce platelet aggregation and adherence of polymorphs to endothelial cells; excess prostaglandin-E_2 can reduce lymphocyte antigen responsiveness. These factors thus promote further immunosuppression commonly found in SIRS and MODS.[33] The use of lipids high in fish oil that contain omega-3 polyunsaturated fatty acids may reduce leukotrines and prostaglandin-E_2 production, as also perhaps reduce the release of interleukin-1 and TNF. These should theoretically benefit patients with evolving MODS.
d. Administration of proteins should not exceed 1–1.25 g/kg per day. The use of preparations with an increased content of branched-chain amino acids has allowed increased nitrogen retention with quick and smooth achievement of nitrogen equilibrium.[34] This is particularly useful in excessively hypercatabolic states during which the patients may lose more than 10 g nitrogen in the urine.
e. Good nutritional support should ensure a rising or normal range of hepatic protein synthesis as judged by plasma albumin and transferrin levels.
f. Administration of vitamins, minerals and trace elements is an integral feature of nutritional support.

Omega-3 fatty acids (found in fish oil), arginine and dietary nucleotides have been combined into special formulated

enteral feeds. A multicentric trial has shown significantly fewer acquired infections, a shorter hospital stay, improvement in protein metabolism and in immune responsiveness in patients receiving these specially formulated feeds.[35]

The above principles of nutritional support are applicable to both enteral and parenteral feeds. Enteral feeds are unquestionably superior, should be started as early as possible, and are always to be preferred.

Support of Organ Systems Viewed in an Overall Perspective

It is important to treat the patient as a whole and not to confine treatment to a specific organ system. This is often lost sight of even in very good ICUs, where superspecialists are very common and where each one thinks exclusively of the organ under his charge. *Not uncommonly the organ survives, but the patient dies. The relative importance of different problems in a patient should never be lost sight of, the one posing the maximum danger needs to be considered as a priority bearing in mind the patient as a whole.*

Nihilistic Approach to MODS

A nihilistic approach to MODS when three or more organs are involved is unjustified and wrong. The prognosis of MODS to an extent depends on the predisposing factors in a given patient, the nature and magnitude of the insult or etiological agent, the nature and magnitude of the host response (about which we know very little), the number and degree of organ involvement but also the combination of organ systems that are dysfunctional.

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CHAPTER 53

Acute Kidney Injury

GENERAL CONSIDERATIONS[1]

The kidneys play a major role in fluid and electrolyte balance, and help to keep the H^+ ion concentration of arterial blood within physiological limits. Renal dysfunction is common in the critically ill, and when present, the morbidity and mortality are both significantly increased. Early detection of renal dysfunction, measures to correct the early dysfunction if this is at all possible, and/or measures to prevent further deterioration in renal function are of great importance in ultimate prognosis. Delay in recognition and management often results in increasing renal failure requiring dialysis till such time as kidney function improves.

Currently, by general consensus, the term acute renal failure (ARF) has been replaced by the term acute kidney injury (AKI). There is some justification in this as AKI takes into account various degrees of injury to the kidneys, whereas the term ARF lacks this concept. The term acute renal dysfunction is perhaps as good as or better than AKI; after all injury causes dysfunction and acute renal dysfunction also implies the possibility of various degrees of dysfunction. In this chapter, AKI and acute renal dysfunction are used synonymously.

An absolute requisite for the diagnosis of renal dysfunction (AKI) is an elevated plasma creatinine concentration. An early sign of renal dysfunction and impending failure is a fall in the urine output. Oliguria is defined as a fall in urine output to less than 400 mL/24 hours, or a fall in urine output to less than 20 mL/hour. *Though oliguria is a frequent accompaniment of AKI, the latter can also occur and progress (with increasing plasma creatinine levels), in the presence of a normal urine output.*

This chapter basically stresses the approach to the diagnosis and management of impending or progressive AKI in ill individuals in an intensive care unit setting. It next briefly deals with the epidemiology of AKI in the ICU and then discusses the current concepts and definitions that help to grade and quantify progressive kidney injury. Following this, there is a description of the bedside approach in the evaluation of acute oliguric kidney injury as also on the medical management and the management by dialysis of established and progressive AKI. The chapter then touches upon important clinical syndromes characterized by severe progressive renal failure; these are invariably critical illnesses requiring intensive care. Finally, there is a brief section on critical illnesses requiring intensive care in patients with underlying chronic renal failure.

CAUSES OF ACUTE KIDNEY INJURY

A rise in serum creatinine and non-protein nitrogenous products generally though not necessarily associated with oliguria can be due to prerenal causes, intrinsic renal disorders and to postrenal conditions characterized by obstruction to the renal outflow system (Box 1).

Acute kidney injury can be due to poor perfusion not severe enough to cause cellular injury or death, to an ischemic or toxic injury to the renal parenchyma, to tubulo-interstitial disease, to glomerular disease leading to impaired filtration, or to obstruction to the renal outflow tract. Azotemia caused by impaired perfusion is termed prerenal azotemia; azotemia caused by intrinsic renal injury is termed renal azotemia; azotemia due to an obstructive uropathy is termed postrenal azotemia. In critical care units AKI is most often due to prerenal causes (impaired perfusion) or due to intrinsic renal damage or injury. However, postrenal obstructive uropathies are also met with and may be easily missed if not kept in mind.

Box 1: Causes of acute kidney injury

- Prerenal causes—
  - Hypovolemia—
    - » Fluid or blood loss
    - » Sequestration of fluid into third space
    - » Loss of effective circulating volume in distributive shock (sepsis, anaphylaxis)
  - Low-output syndromes with poor pump function and low cardiac output
- Intrinsic renal diseases—
  - Acute tubular necrosis (after shock, sepsis, severe hemolysis or surgery)
  - Acute cortical necrosis
  - Toxic factors (drugs, heme pigment, contrast media)
  - Acute interstitial nephritis
  - Acute glomerulonephritis; acute pyelonephritis; other acute nephritic syndromes
  - Vascular causes (vasculitis, obstruction to large vessels, TTP, DIC, HUS, HPS, malignant hypertention)
  - Crystal precipitation (acute uric acid nephropathy)
  - Plasma cell dyscrasias (e.g. tubules obstructed by myeloma protein)
- Postrenal causes—
  - Ureteral or bladder outlet obstruction—mitotic lesions retroperitoneal fibrosis, calculi, hypertrophic prostate, Ca prostrate
  - Traumatic rupture of the bladder with extravasation of urine

Abbreviations: TTP, thrombotic thrombocytopenic purpura; DIC, disseminated intravascular coagulation; HUS, hemolytic-uremic syndrome; HPS, hemophagocytic syndrome.

Prerenal Causes

Prerenal causes act by inducing a fall in perfusion pressure within the vessels perfusing the kidneys. Important prerenal causes are hypovolemia, low-output syndromes related to acute heart failure, and severe vasodilatation with a reduction in the arterial blood pressure and perfusion pressure within the kidneys.

Hypovolemia has been discussed in an earlier chapter (see Chapter Fluid and Electrolyte Disturbances in the Critically Ill). It can be due to loss of extracellular fluid as in vomiting, diarrhea, burns and blood loss. Hypovolemia can also result from sequestration of fluid in the third compartment as in intestinal obstruction, pancreatitis, peritonitis, post intra-abdominal surgery and crush injuries to muscles. A fall in effective circulating volume also occurs in distributive shock (sepsis and anaphylaxis), characterized by peripheral vasodilatation, hypotension and a fall in renal perfusion.

Poor pump function of the heart, due to any etiology, is also an important cause of prerenal azotemia.

Intrinsic Renal Disorders

The *three important renal disorders* causing acute oliguric kidney injury in an ICU setting are—

1. Acute tubular necrosis (ATN).
2. Drug toxicity particularly related to the use of aminoglycosides.
3. Acute interstitial nephritis either allergic or infectious in etiology.

An important cause of ATN is prolonged unrelieved renal ischemia as in shock, severe sepsis and major surgery. Toxic causes as in poisoning can also result in ATN. Acute severe hemolysis results in ATN because of the toxic effect of heme pigments on renal tubular cells, blockage of renal tubules by pigment casts and impaired perfusion of kidneys. Acute glomerulonephritis and other nephritic syndromes are also important causes of AKI, but are uncommon in an intensive care setting. Acute fulminant pyelonephritis is at times a feature of urosepsis and results in AKI. Renal vascular disorders causing AKI, though again uncommon in the ICU, are easily missed. They include obstruction to large renal vessels (embolism or thrombosis) or to small vessels as in vasculitis of any etiology, thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS), hemophagocytic syndrome and malignant hypertension. In oncology units, acute oliguric renal injury is observed following precipitation of uric acid within urinary tubules causing an acute uric acid nephropathy. Plasma cell dyscrasias (in particular myeloma) may present with quickly evolving renal dysfunction due to obstruction of renal tubules by protein deposits and to interstitial nephritis.

Drug toxicity causing interstitial nephritis is an important cause of AKI and ARF in the ICU. The need for taking a proper history of drugs the patient has received cannot be overstressed. Radiocontrast agents, aminoglycosides, amphotericin, nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors are the drugs most frequently observed to precipitate AKI. NSAIDs and ACE inhibitors induce a form of prerenal azotemia. NSAIDs inhibit cyclooxygenase, leading to a depletion of eicosanoids, which normally counteract the constrictive effect on afferent arteriolar tone due to increased renal adrenergic drive and lipid derived constrictors. Severe afferent arteriolar vasoconstriction in AKI can occur particularly in the presence of hypotension, volume depletion, sepsis or heart failure. ACE inhibitors reduce angiotensin II levels, leading to a lowering of renal perfusion pressure and a dilatation of efferent arterioles. This lowers glomerular filtration pressure and causes AKI, particularly in patients with bilateral renal artery stenosis or in unilateral renal artery stenosis with a contralateral diseased kidney. Generally, the prerenal azotemia induced by NSAIDs and ACE inhibitors is reversible if the drug is promptly stopped. The use of contrast media for imaging purposes is an important cause of acute renal injury. Contrast media act by causing renal vasoconstriction and medullary ischemia, as also by a direct toxic effect on renal tubules. Patients, who are volume depleted, diabetics and those with background renal disease, are at high risk to develop renal toxicity.

Box 2: Risk factors for acute kidney injury

- Age of onset >60 years
- Sepsis
- Cardiovascular failure
- Liver cirrhosis
- Respiratory failure
- Chronic heart failure
- Lymphoma or leukemia

Source: de Mendonça A, Vincent JL, Suter PM, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Medicine. 2000;26(7):915-21.

Box 3: Risk factors for increasing mortality in acute kidney injury

- Age >65 years
- Male gender
- Acute oliguric renal failure
- Sepsis
- Nonrenal organ failure
- Thrombocytopenia
- Mechanical ventilation
- Associated comorbid states

Postrenal Conditions

Postrenal disorders include obstructive lesions within the renal outflow system. They include papillary necrosis, ureteric obstruction by calculi or retroperitoneal fibrosis or tumors, and bladder outlet obstruction commonly observed with prostatic hypertrophy and in prostate cancer. Extravasation of urine as after rupture of the bladder is another postrenal disorder presenting with acute oliguric kidney injury. Obstruction is an uncommon but important cause of acute oliguric renal injury, and should be considered in all patients who are known to have a solitary functioning kidney. Intrarenal obstruction to urine flow due to obstruction of renal tubules from various causes has been considered under intrinsic renal disorders.

EPIDEMIOLOGY

In the ICU, AKI is more often than not a feature, a part and parcel of multiorgan failure. It occurs quite frequently, being present in about 30% of ICU patients.[2-4]

The most common cause of intrinsic renal failure in the ICU is ATN, which is generally due to two important causes. These are poor renal perfusion as observed in hypotensive states and shock from any cause, and sepsis. Impaired perfusion often leads to prerenal azotemia, but if impaired perfusion persists for long and stands uncorrected, or if there is a very sharp fall in perfusion due to marked hypotension for even a brief period, as is seen, for example, during major surgical procedures, ATN may well result. Sepsis is an equally important cause of ATN and is in part due to action of cytokines on renal structure and function. ATN can also occur secondary to the use of nephrotoxic antibiotics, as a postsurgical complication and following the use of contrast media. The etiology of ATN can well be multifactorial as is often observed in sepsis, where hypotension, the noxious effect of cytokines, the use of nephrotoxic antibiotics and use of contrast dyes for imaging may all play a varying role to result in ATN.

It is a common observation that in a patient who has multiorgan failure but in whom kidney function for some reason is well preserved, the prognosis for recovery is better than in a patient with multiorgan failure which also involves the kidney. This observation may be misleading as severe renal involvement in multiorgan failure may merely be a marker of the severity of the illness, which could be associated with an increased mortality. Recent studies have however observed that AKI does in fact, contribute to mortality in the setting of contrast nephropathy and cardiac surgery.[5,6]

Increasing renal dysfunction, i.e. increasing severity of AKI leads to a worsening prognosis and increasing mortality. As will be explained later, RIFLE (risk, injury, failure, loss and end-stage kidney disease) severity grades correspond to increasing mortality. It has been reported that patients with a maximum score of RISK have a mortality rate of 8.8% as compared to a mortality rate of 11.4% for INJURY, and a mortality rate of 26.3% for FAILURE. Patients who did not have AKI had a mortality rate of just 5.5%.

Risk Factors for Developing Acute Kidney Injury in the Intensive Care Unit

Mendonca and associates[7] observed that there was a high risk of developing AKI if the patient has the following seven characteristics on admission. These are indicated in Box 2.

Risk Factors for Increasing Mortality in Acute Kidney Injury

These include an older age greater than 65 years, male gender, acute oliguric renal failure, sepsis, nonrenal organ failure, thrombocytopenia, mechanical ventilation, associated comorbid states (Box 3).

The most important risk factor contributing to increased mortality in AKI is the associated failure of other organ systems, notably the cardiovascular, respiratory and hepatic. This is a universally accepted fact. However, the mortality figure with increasing organ failure varies in different studies. Liand and colleagues[8] noted a mortality of 53% with two organ failures, 80% with three organ failures and 100% with five organ failure. This does not hold true with reference to multiorgan failures related to the severe tropical infections (see Chapter Multiple Organ Dysfunction Syndrome and Chapter Community-Acquired Fulminant Infections Requiring Critical Care).

DEFINITIONS

It is important to be aware of changing concepts in relation to ARF. The conventional definition of ARF is an acute decrease

Table 1: Acute kidney injury staging: the RIFLE system

Stages	*Serum creatinine increase*	*Urine output criteria*
Risk	≥150–200%	<0.5 mL/kg per hour for >6 hours
Injury	>200–300%	<0.5mL/kg per hour for >12 hours
Failure	>300% or serum creatinine >4 mg/dL or GFR decrease by 75%	<0.3 mL/kg per hour for >24 hours or anuria >12 hours
Loss	Complete loss of kidney function >4 weeks	
End-stage	Complete loss of kidney function >3 months	

Abbreviation: GFR, glomerular filtration rate.

Table 2: Acute kidney injury staging: the AKIN system

Stages	*Serum creatinine increase*	*Urine output criteria*
I	≥0.3 mg/ dL or ≥150–200%	<0.5 mL/kg per hour for >6 hours
II	>200–300%	<0.5 mL/kg per hour for >12 hours
III	>300% or acute renal replacement therapy	<0.3 mL/kg per hour for >24 hours or anuria >12 hours

Source: Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.

in renal function characterized by an abrupt fall in the glomerular filtration rate (GFR), with retention of creatinine, urea and other waste products in the blood, together with a disturbance in the fluid and electrolyte metabolism of the body.

Renal dysfunction however can be mild, moderate or severe and the above definition takes no account of this all important clinical fact. In other words, the conventional definition does not allow one to quantify or characterize renal failure and has therefore been a hindrance to both clinical and basic research in this field.

The term AKI was proposed in preference and as an alternative to ARF by the Acute Kidney Injury Network (AKIN) so as to take into consideration the entire range of renal dysfunction. This concept was based on data showing that even very mild renal dysfunction, characterized by a small increase in serum creatinine influences outcome. The Acute Dialysis Qualitative Initiative (ADQI) developed subsequently evidence-based guidelines for prevention and treatment of ARF so as to allow comparison of results between different study groups and to advance research.[9] This group proposed a consensus categorized definition—the RIFLE criteria. These criteria quantified ARF and were validated and shown to correlate with hospital mortality and patient outcome in several large studies. Following the RIFLE criteria, AKIN proposed a revision of the RIFLE criteria[10-12] so as to take into consideration smaller changes in creatinine not taken into account by RIFLE. The RIFLE and AKIN criteria are given in Table 1 and Table 2.

There are certain differences between the RIFLE system of staging and the later introduced AKIN system.

- The AKIN system (Table 2) recognizes three stages—
  - Stage 1: corresponded to stage R of the RIFLE system.
  - Stage 2: corresponded to stage I of the RIFLE system.
  - Stage 3: corresponded to stage F of the RIFLE system.
- The diagnosis of AKI in the AKIN staging could be made if the serum creatinine rose by just 0.3 mg/dL from the baseline or if there was oliguria for more than 6 hours. However, there should be adequate volume replacement and urinary tract obstruction should be excluded before the low urine output is taken as a marker for AKI. It should be kept in mind that oliguria as a marker for AKI can be misleading as nonoliguric AKI is commonly observed in the ICU.

The importance of taking into consideration the absolute rise in creatinine was based on the finding in several studies that such increments in serum creatinine are associated with a high mortality.

The AKIN staging system states that the increments of serum creatinine described in stages 1, 2 and 3 should occur during a period of no more than 48 hours, compared to 7 days laid down in the RIFLE system.

The RIFLE and AKIN criteria for AKI help to identify patients with increased risk of death and renal replacement therapy.[9,10,13] The greater the increase in staging of AKI in a patient or in a group of patients, the greater the risk of death. There is evidence[14] that even after AKI resolves there is an increased risk of cardiovascular disease or chronic renal disease and mortality in these patients.

In the following further discussion on AKI, the term ARF when used signifies AKI, sufficiently severe to reach the "failure" stage of the RIFLE staging or stage III of the AKIN staging system.

There has been for some years a search for biomarkers to predict impending AKI as also to assess the severity of injury. Identification of impending or early AKI through the use of appropriate biomarkers could be useful as intervention may perhaps help to stop or control it. Biomarkers that are being researched upon are serum cystatin C, urine interleukin (IL) 18, tubular enzymes such as N-acetyl-glucoaminidase, neutrophil gelatinase-associated lipocalm (NGAL) and kidney injury molecule. Further research is necessary to validate the use of these markers for diagnostic purposes. *NGAL is the biomarker most commonly used to identify patients with early kidney injury, even before there is a rise in the serum creatinine.*

BEDSIDE APPROACH FOR THE EVALUATION OF ACUTE KIDNEY INJURY IN THE ICU (BOX 4)

Acute kidney injury generally comes to the attention of the physician either because of the finding of a raised serum creatinine or blood urea nitrogen (BUN) level or because of oliguria. It needs to be however restressed that all forms of AKI—prerenal, renal and postrenal—can be nonoliguric in nature. A normal urine output is therefore not a reliable indicator of adequate renal function. As pointed out earlier, nonoliguric kidney injury is particularly observed following

Box 4: Evaluation of a patient with acute kidney injury

- Thorough clinical examination with maintenance of input/output charts—
  - History of administration of nephrotoxic drugs or nephrotoxic insult in the recent past
- Urine analysis
- Serum creatinine and BUN levels; creatinine clearance test
- Other urinary and blood indices of renal function—urine osmolality
- Urinary sodium (mEq/L) fractional excretion of sodium
- Evaluation of circulatory hemodynamics
- Imaging studies—particularly for kidney size, uropathy
- Renal biopsy (in rare selected problems)

Abbreviation: BUN, blood urea nitrogen.

the use of aminoglycosides. The approach to diagnosis and management in both oliguric and nonoliguric AKI is similar. A patient with AKI who is nonoliguric is at an advantage compared to the oliguric patient because fluid and electrolyte management is easier. There is a greater leeway for fluid administration and lesser danger of fluid overload.

Clinical Evaluation

A clinical evaluation is always of utmost importance—

- The background factors and the etiology of oliguria with azotemia should be ascertained through a careful history, a thorough clinical examination and other relevant investigations. Intake/output charts should be evaluated. The role of nephrotoxic drugs should be kept in mind. The history of a recent hypotensive episode or a recent nephrotoxic insult, for example, the use of a contrast dye in radiological investigations, is an important pointer to the cause and nature of AKI.
- In a patient admitted to the ICU with a rise in serum creatinine, it is important to determine whether the renal injury is acute or chronic. A sudden oliguria always points to an acute disturbance in renal function.
- It is vital to determine whether oliguria with azotemia is due to prerenal factors, due to intrinsic renal disease or due to postrenal causes. All prerenal causes of oliguria, if left uncorrected, have the potential to cause intrinsic renal damage (ATN). Hence the presence of prerenal etiological factors by no means exclude intrinsic renal damage. For this a careful evaluation of the urine should be performed as outlined below.

Urine Evaluation

When diminished renal perfusion is the cause of oliguria with azotemia, there is an increase in sodium reabsorption by the renal tubules with a marked decrease in urinary sodium excretion to usually below 20 mEq/L. The urine osmolality is higher than 500 mOsm/kg H_2O. An examination of urinary sodium concentration of a random urine sample is therefore of great help.

Conversely, intrinsic renal disease causing acute oliguric renal injury (as in ATN) is associated with impaired sodium absorption by the renal tubules, with an increase in the urinary excretion of sodium. A random urine sample in these patients generally shows a urine-sodium concentration of above 40 mEq/L. Urine concentrating ability is also abnormal, resulting in isosthenuria and a urine osmolality less than 350 mOsm/kg H_2O.

There are however certain important provisos to the above statements. A urinary sodium greater than 40 mEq/L or more can occur in prerenal azotemia and oliguria if the effect of a recently given diuretic persists, in patients who have coexisting tubular abnormality, or in patients who have chronic renal disease characterized by impaired sodium absorption. A higher urinary sodium excretion can also be due to the presence of nonabsorbable anionic substances in the urine, such as bicarbonate in patients with metabolic acidosis, and certain penicillins which obligate the excretion of cations like sodium. Use of osmotic diuretics like mannitol will also result in increased sodium excretion. Finally, elderly persons can also show a comparatively high urinary sodium excretion in the presence of diminished renal blood flow. Therefore, though the urinary sodium concentration is an important pointer that helps distinguish prerenal from renal azotemia, it should not be considered in isolation. All the factors listed above should be taken into consideration before arriving at a responsible conclusion.

Fractional Excretion of Sodium

The fractional excretion of sodium (FENa) represents the fraction of sodium filtered at the glomerulus that is excreted in the urine.[15] It is determined by comparing the urinary sodium clearance to the urine creatinine clearance.

$$\text{FENa} = \frac{\text{U/P Na}}{\text{U/P Cr}} \times 100$$

where U is the urinary concentration and P the plasma concentration. In prerenal azotemia, the FENa is less than 1%; in AKI due to renal causes, it is greater than 2%.

The FENa is the best and most reliable single urinary test for AKI,[15,16] but again should not be considered in isolation. Acute oliguric kidney injury following the use of contrast agents, rhabdomyolysis, myoglobinuria and sepsis can be associated with the FENa less than 1%.[15]

In patients with prerenal azotemia, the use of diuretics will obscure the significance of the FENa values. In these patients the fractional excretion of urea or a urine to plasma ratio of creatinine higher than 40 is indicative of prerenal azotemia.[17]

Microscopic Examination of the Urine

Microscopic examination of the sediment of a freshly voided urine sample is elementary but of great value.

- The presence of tubular epithelial cells and of epithelial cell casts (in particular muddy brown casts) suggests ATN.
- In prerenal azotemia, the urinary sediment shows non-specific hyaline casts or finely granular casts.

Table 3: Laboratory findings distinguishing prerenal azotemia from acute tubular necrosis (ATN)

Parameters	*Prerenal azotemia*	*ATN*
Urine sodium (mEq/L)	<20	>40
Urine/plasma creatinine	>40	<20
Fractional excretion of Na	<1	>2
Urine sediment	Normal or nonspecific hyaline casts	Renal tubular epithelial casts, muddy brown casts

- In acute interstitial nephritis the urine shows many white blood cells and white blood cell casts.
- In acute glomerulonephritis and in any other pathology causing the "nephritic syndrome" the urine contains albumin, plenty of red blood cells, white blood cells and above all red blood cell casts.
- The presence of bacteria with a positive culture showing a high colony count, points to an infection in the urinary tract.
- Modest proteinuria (up to 1 g/dL) is common in many forms of AKI, but proteinuria in the nephrotic range (>3.5 g/dL) is most often due to glomerular disease, except when associated with Bence-Jones proteinuria in multiple myeloma. Urine protein electrophoresis will distinguish between Bence-Jones protein and albumin in a suspected case of multiple myeloma (Table 3).

Determining Degree of AKI

In patients with AKI it is important to determine the degree of renal dysfunction and also to determine the changes in the internal milieu brought about by renal dysfunction.

Blood Creatinine Levels

This is the simplest and most valuable guide to renal dysfunction. It is currently accepted that even a rise as little as 0.3 mg/dL above the base line signifies renal dysfunction and injury. Even so, the normal GFR must be reduced by about half before there is a significant rise in the serum creatinine levels. Modest degrees of renal dysfunction may thus go undetected if a creatinine clearance test is not done. During the acutely evolving phase of renal injury, serum creatinine levels may rise by 2 mg/dL every 24 hours. More rapid increases can occur in rhabdomyolysis. A misleading increase in serum creatinine without a fall in the GFR may occur when cephalosporin or certain ketones (acetoacetate) interfere with the calorimetric method used for its measurement.[18] Cimetidine and trimethoprim-sulfamethoxazole compete with tubular secretion of creatinine and result in increased creatinine values without a fall in the GFR.[18]

Blood Urea

Urea is the major nitrogen-containing metabolite of protein metabolism and is excreted chiefly by the kidneys. About 35–50% of filtered urea is reabsorbed by the tubules. In the presence of hypovolemia or decreased renal perfusion from any prerenal cause, the reabsorption of urea can increase to as high as 90%. In contrast, creatinine is not reabsorbed by the renal tubular cells. When measured as BUN in mg/dL, the normal ratio of BUN to creatinine in serum is 10:1. An increase in this ratio to 20:1 or more points to prerenal azotemia. Blood urea levels are also related to the amount of protein intake and degree of protein catabolism. Inadequate caloric intake, corticosteroid administration, and the stress of a hypermetabolic critical illness can result in endogenous protein catabolism, and increase in blood urea levels even with normal renal function. GI hemorrhage with the resulting absorption of blood protein is another important cause of elevated blood urea levels (Box 5).

Box 5: Causes of elevation of BUN or serum creatinine elevation without reduction in the glomerular filtration rate

- Increased urea levels—
  - GI bleeding
  - Hypercatabolic illnesses—burns, high fever, tetanus, seizure disorders
  - Increased protein intake or parenteral nutrition
  - Drugs: corticosteroids
- Increased creatinine levels due to increased biosynthesis of creatinine—
  - Rhabdomyolysis
  - Drugs: cimetidine interferes with tubular creatinine secretion

Abbreviation: GI, gastrointestinal.

Creatinine Clearance Test

Creatinine clearance test using a 24-hour urine collection is a reliable index of renal function.

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Urine creatinine (mg/dL)} \times \text{Urine volume (mL/min)}}{\text{Serum creatinine (mg/dL)}}$$

Other Urinary and Blood Indices

Other urinary and blood indices are often used to distinguish between prerenal azotemia and acute oliguric renal injury. The urine osmolality, the urine/plasma urea nitrogen ratio, and the urine/plasma creatinine ratio increase in prerenal azotemia, whereas urine sodium and the fractional excretion of filtered sodium remain low. The indices which help to distinguish between prerenal azotemia and azotemia due to intrinsic renal causes (as in ATN) have already been discussed earlier.

Serum Electrolytes

Estimation of serum sodium, potassium, chloride, bicarbonate, calcium, magnesium and phosphate should be done. Their monitoring forms an important feature in the management of AKI.

Arterial pH and Blood Gas Analysis

It should always be done to determine the presence and degree of acidosis, as also to determine any abnormality in blood gas exchange within the lungs.

Evaluating Circulatory Hemodynamics

The hemodynamics of the circulation should be carefully evaluated. A central venous line is invariably inserted in these patients and provides a guide to the central venous pressure. In oliguric patients, it is important that the filling pressures are maintained at an optimal level. When there is doubt about hypovolemia with low left-sided filling pressures contributing to azotemia, a Swan-Ganz catheter may need to be inserted to determine the pulmonary capillary wedge pressure. A volume load can then be so adjusted as to keep this wedge pressure around 12–15 mm Hg.

Imaging Studies

- An ultrasound imaging is invaluable for the following reasons—
  1. It gives the size of the kidneys—small kidneys suggest underlying chronic renal disease.
  2. It can pick up ureteric obstruction and hydronephrosis, and is invaluable in the diagnosis of oliguria due to postrenal causes.
  3. In fulminant urinary infections, an ultrasound examination helps in the detection of a renal or perinephric abscess.
- An abdominal X-ray demonstrates the presence of radio-opaque kidney stones and may pick up other associated diseases within the abdomen.
- Imaging studies involving the use of contrast dyes are contraindicated in ARF because of the toxicity of the contrast dye to the kidneys. A retrograde pyelography may however be necessary in patients with obstruction to the ureter resulting in postrenal oliguria and renal failure. A computed tomography study may help to localize a perinephric abscess or diagnose a fulminating pyelonephritis.

Renal Biopsy

A renal biopsy is avoided in critically ill patients with ARF except—

- When there is strong suspicion of acute vasculitis, or a rapidly evolving autoimmune disorder and
- In patients with ATN in whom renal failure fails to resolve within 6–8 weeks.

MANAGEMENT PROTOCOL FOR ACUTE OLIGURIA IN CRITICALLY ILL PATIENTS

- It is important to ensure that urinary catheters in critically ill patients do not get blocked, thereby giving a false impression of oliguria.
- It is vital to ensure that the hemodynamic status of the patient is satisfactory. He should have a normal circulating volume, normal filling pressures in the right and left heart chambers and an adequate cardiac output. In critically ill patients, on rare occasions, one may have to ascertain this with a Swan-Ganz catheter and give enough volume infusion to maintain the pulmonary capillary wedge pressure around 15 mm Hg. The pump in other words must be optimally primed.

  If oliguria persists despite the pump being fully primed, and if facilities so exist, the cardiac output should be measured. If this is found to be low, the cause of this should be ascertained. Cardiac output can be increased by using inotropic support with dopamine (5–10 μg/kg per minute) or dobutamine (10–20 μg/kg per minute); at times both can be used together.

  If the cardiac output is normal or high, but the patient is hypotensive as with sepsis or other forms of distributive shock, the vascular resistance is increased with dopamine at 10–15 μg/kg per minute or the use of nor-epinephrine or vasopressin.
- Whilst the patient's hemodynamic state is brought to as optimal a level as possible, a clinical assessment and the urinary evaluation described earlier is simultaneously carried out to determine if there is any intrinsic renal damage causing ARF. The importance of estimating urinary sodium concentrations and FENa values has already been emphasized.
- The persistence of oliguria with an increase in serum creatinine levels in the presence of normal hemodynamics suggests AKI. An attempt is often made at this stage to induce an increased urine output through the use of loop diuretics given as a continuous titrated intravenous (IV) infusion. The use of both IV loop diuretics and of low-dose dopamine in the management of AKI is discussed in the next Section "Management of Persistent Oliguric AKI".

Drugs in Patients with Persistent Oliguria

All nephrotoxic drugs should be withheld. Aminoglycosides in particular should always be stopped right at the start when oliguria and azotemia first appear. Carbapenems and aztreonam are effective in countering Gram-negative sepsis including that due to *Pseudomonas pyocyaneus*. If amphotericin B is being used to counter systemic fungal infections, the drug should be stopped and an alternative non-toxic or less nephrotoxic anti-fungal used. If this is not possible, it should be used at half or quarter of the usual dose. A list of drugs which are preferably stopped or not administered in ARF is given in Box 6.

If for any reason it is necessary to administer drugs that are nephrotoxic, their dosage is modified as per the creatinine clearance. A list of common ICU drugs excreted by the kidneys, with modifications in their dose, is detailed in Table 5 of Chapter Antibiotic Therapy in the Intensive Care Unit.

Box 6: Drugs which should be discontinued in acute renal failure (alternative drugs in parenthesis)

- Nephrotoxic drugs—
  - Aminoglycosides (imipenem/aztreonam)
  - Amphotericin B (fluconazole)
  - Pentamidine (trimethoprim-sulphamethoxazole)
- Drugs causing allergic interstitial nephritis—
  - Penicillin and allied drugs (erythrocin/vancomycin)
  - Cephalothin, vancomycin
  - Trimethoprim-sulphamethoxazole (pentamidine)
  - Cimetidine (sucralfate, other antacids)
  - Nonsteroidal anti-inflammatory drugs (paracetamol)

MANAGEMENT OF PERSISTENT OLIGURIC AKI

Prevention

The poor outcome of patients suffering from progressive AKI has led to the trial of several drugs both with the view to prevent and/or ameliorate the condition. Preventive measures have been tried in particular with regard to the frequent occurrence of contrast-induced nephropathy. IV furosemide and IV mannitol both as preventive and treatment of contrast induced nephropathy have led to worse outcomes. Dopamine and atrial natriuretic peptide have also proved ineffective. Acetylcysteine and fenoldopam have been found to decrease the incidence of contrast-induced nephropathy in high risk patients. *The current recommendation for prevention of contrast-induced nephropathy, particularly in high-risk patients, is adequate hydration with normal saline or sodium bicarbonate, 1,200 mg of acetylcysteine twice daily on the day before and the day of the procedure and the use of low osmolar contrast media.*

Dopamine in AKI

Dopamine has long been used in the prevention and treatment of AKI. It has now been shown that dopamine is ineffective and should not be used. In patients with early renal dysfunction, renal creatinine higher than 1.8 mg/dL and urine output less than 0.5 mL/kg per hour, dopamine neither alters peak creatinine values nor decreases the need for renal replacement therapy nor reduces mortality. Besides being clinically ineffective, the drug can produce harmful side effects—arrhythmias, myocardial and gut ischemia. *Currently, the drug has no role in the prevention and treatment of AKI.* Low dose (2–3 μg/kg per minute) may induce a diuresis in some patients with AKI but this in no way improves ultimate outcome. The most the drug can do through its diuretic action is to allow a better leeway for the management of fluid and electrolyte balance.

Furosemide in AKI

Diuretics, in particular loop diuretics like furosemide are frequently used in AKI in an attempt to increase urine flow and convert oliguric into nonoliguric AKI, the latter entity having a better prognosis. Current work has observed that though the use of loop diuretics in early or established AKI allows a better management of fluid, electrolyte (in particular of hyperkalemia or hypercalcemia) balance, there is no proven role of these diuretics either in prevention or management of AKI. *If therefore furosemide is used temporarily to allow better fluid electrolyte management, it should not be allowed to delay the initiation of renal replacement therapy if this is indicated.*

Atrial Natriuretic Peptide

Short-term benefits of atrial natriuretic peptide (ANP) (BNP type natriuretic peptide) on perioperative renal function include lesser rise of creatinine, a lesser reduction of GFR and a greater urine output after surgery. The drug cannot be recommended until further studies have proven its use.

SUPPORTIVE TREATMENT

The treatment of AKI is unfortunately merely supportive.

The principles of management are—

- To maintain body homeostasis with particular reference to fluid, electrolyte and acid-base balance.
- Hemodynamic management to restore and maintain hemodynamic stability.
- To maintain nutrition.
- To recognize and treat complications occurring in the course of the illness.
- To use specific treatment for some forms of acute glomerulonephritis.
- To use dialysis when indicated, and to decide on the type of dialysis best suited to the patient.

Maintaining Homeostasis

Acute tubular necrosis is the most common form of oliguric ARF observed in critical care units. The oliguric phase may last for a period ranging from a few days to as long as 4–6 weeks. This is followed by a period or phase of relative diuresis.

Fluid Balance

The greatest danger is fluid overload. The fluid intake should not exceed the urine output plus the fluid output from other sources (e.g. nasogastric suction, fluid loss from diarrhea, sweating, surgical drains) plus the insensible water loss. In a well-nigh anuric patient who has no fluid loss from other sources, the fluid intake should not exceed 500–700 mL.

In a patient who already has been in oliguric renal failure some days prior to admission to the ICU, it is often impossible to determine the degree of fluid imbalance present prior to hospitalization. In these patients, as also in critically ill patients in whom AKI amounting to ARF is a complication of severe underlying disease (e.g. acute lung injury or sepsis), it is often necessary to measure the central venous pressure through a central venous catheter, and occasionally in complicated problems, the left heart pressures through a

Box 7: Sodium content of important body fluids

- Sweat: Na^+ 20–100 mEq/L
- Gastric fluid: Na^+ 30–90 mEq/L
- Diarrhea: Na^+ 50–110 mEq/L
- Small bowel ostomy: Na^+ 70–150 mEq/L
- Biliary drainage: Na^+ 120–170 mEq/lL

Swan-Ganz catheter. The left heart pressures if measured should not exceed 15–18 mm Hg.

Critically ill patients may require large quantities of IV fluids for hyperalimentation, administration of vasopressors and antibiotics. Fluid overload is certain in these patients and methods involving dialysis are then necessary to ensure that fluid overload does not occur.

Sodium Balance

Sodium balance is maintained by replacing the sodium that is lost. Urinary losses of sodium can be exactly measured by 24 hour collection of urine. An approximate method of estimating urinary sodium loss is by determining the sodium concentration in a random sample and multiplying this by the urine volume over 24 hours. GI losses are difficult to measure but can be roughly estimated. The approximate sodium content of body fluids is given below in Box 7.

In oliguric renal failure, hyponatremia is the most frequent electrolyte abnormality; this is invariably a dilutional hyponatremia due to a fluid overload.

Potassium

Except in individuals who lose a large quantity of fluid through nasogastric suction or diarrhea, hyperkalemia is always to be anticipated and promptly corrected. Potassium should be invariably restricted in these patients except in those who have potassium losses from the above-mentioned sources (see Section Fluid and Electrolyte Disturbances in the Critically Ill).

Acid-Base Balance

Uremic acidosis is an expected feature of oliguric renal failure, and is related to protein catabolism. 1 mEq of H^+ ion is retained for every gram of protein catabolism, and on a normal diet, 70 mEq of H^+ ions are produced in the body. With poor renal function H^+ ions accumulate and cause acidosis. Patients may develop a substantial base deficit higher than 15 mEq/L, and the pH may drop to below 7.2 in spite of a compensatory fall in the $PaCO_2$ produced by hyperventilation. It is necessary to correct significant acidosis with 50–100 mEq of IV sodium bicarbonate (see Chapter Acid-Base Disturbances in the Critically Ill). If serum calcium levels are low, it is prudent to administer 10 mL of calcium gluconate intravenously before administering sodium bicarbonate.

Lactic acid acidosis often occurs in critically ill patients with severe kidney injury amounting to ARF, particularly in those with sepsis. Lactic acid production in very ill patients may be as high as 50 mEq per hour, and can reduce plasma bicarbonate at the rate of 1–2 mEq/L per hour. In the presence of marked oliguria, replacement of large quantities of bicarbonate almost always results in fluid overload and in hypernatremia, requiring dialysis. All efforts should be made to optimize oxygen transport and tissue perfusion in these patients.

Calcium, Magnesium and Phosphates

It is important to maintain these electrolytes within normal limits. Hypocalcemia may occur following the use of IV bicarbonate, but otherwise tetany is rare. Hypercalcemia is observed in kidney injury associated with multiple myeloma.

Magnesium excretion is reduced, and magnesium containing antacids should be avoided.

Phosphate levels increase with increasing duration of oliguric renal failure. When serum phosphate levels exceed 6 mg/dL, aluminum hydroxide 30 mL 8 hourly is effective in binding phosphates within the gut. Once phosphate levels are less than 6 mg/dL, calcium carbonate can be given in a dose of 500 mg 8 hourly, after meals.

If IV alimentation is used for the purposes of nutrition, it is best to avoid phosphates in the IV fluids till such time as the high phosphate levels have returned to normal.

Maintaining Hemodynamic Stability

Appropriate management to ensure hemodynamic stability is of paramount importance. The tendency to overinfuse fluids in the early stage of AKI is to be avoided as it can result in pulmonary congestion and ultimately to ARDS. Not uncommonly AKI is part and parcel of a multiorgan dysfunction syndrome which includes cardiovascular dysfunction. Complicated problems require not only a central venous pressure (CVP) line, but also a Swan-Ganz catheter to estimate left sided filling pressures. These pressures are to be considered as guides to fluid replacement, yet sometimes can be misleading. *Noncardiogenic pulmonary edema can occur even when the left sided filling pressures are within normal limits. If this is not promptly realized a full blown ARDS may complicate the situation.*

Maintain Nutrition[19]

In an intensive care setting, patients with oliguric AKI are invariably catabolic. It is important to minimize negative nitrogen balance. Overfeeding unfortunately does not for several reasons correct the negative nitrogen balance. In fact, it is better to underfeed than overfeed these patients. The total caloric requirement should be 20–30 kcal/kg per day. Increasing caloric intake above this level not only fails to correct nitrogen balance but also induces hyperglycemia and hypertriglyceridemia and a positive fluid balance.

The mechanism of increased catabolism in these patients is increased insulin gluconeogenesis fuelled by protein catabolism. Liberation of proinflammatory cytokines and catecholamines contributes further to the catabolic state.

Enteral feeding is the preferred form of nutritional support as it helps preserve the integrity of the gut. In the past, protein restriction was advised to control uremic symptoms, but this can do more harm than good, as it can cause a marked negative nitrogen balance. In patients with AKI who do not need dialysis a protein intake of 0.8–1 g/kg per day is adequate. In patients with AKI on renal replacement therapy an intake of 1–1.5 g/kg per day is advisable. There are many who advocate a large protein intake but this could again do more harm than good; also a larger protein intake does not get rid of the negative nitrogen balance.

The rest of the calorie requirement is divided roughly between carbohydrates and fats. Essential fatty acids such as omega-3 polyunstaurated fatty acids and aminoacids, such as arginine, have been found to stimulate the immune system and are believed to be beneficial.

If for any reason enteral feeds are not possible, parenteral feeding should be started early. This is of essence in the management of severely catabolic patients with marked AKI. All such patients require dialysis or hemofiltration to allow necessary administration of increased quantities of fluid associated with parenteral nutrition and to allow a larger protein intake without producing uremic symptoms. Appropriate nutritional support is vital as it helps in renal recovery and improves overall survival in AKI.

Recognize and Treat Complications

Complications may arise as a result of the primary disease causing ARF, or may be directly related to ARF. Rapidly progressive ARF has a high morbidity even when it occurs as a primary event. It can ultimately so derange homeostatic mechanisms, as to lead to multiple organ failure and death.

Important complications associated with acute oliguric renal failure are listed in Box 8. They should be anticipated, if possible prevented, and when they do occur, should be promptly treated.

Dose adjustments of all drugs during acute oliguric renal failure are of great importance, else drug toxicity is inevitable. Uremic patients bleed easily. GI bleeding is common; bleeding from other sites due to platelet dysfunction also occurs. If this is observed, or if more effective hemostasis is required for any operative or invasive procedure, the prophylactic use of desmopressin acetate 0.3 µg/kg intravenously or the use of sufficient quantity of cryoprecipitate and platelet concentrates shortens the bleeding time appreciably. Prophylaxis against GI bleeding due to acute erosive gastritis is generally recommended. Sucralfate is preferable to the use of other antacids. In the presence of active bleeding, a H_2-antagonist or omeprazole should be used.

Kidney recovery in ATN is heralded by the onset of the diuretic phase. In some patients diuresis may be as high as 5–6 L/day. Blood creatinine and urea may remain high for some days in spite of the diuresis. Fluid and electrolyte balance should be maintained as per the principles outlined above. With progressive recovery, homeostasis is finally achieved.

Box 8: Complications associated with acute kidney injury

- Metabolic—
  - Hyperkalemia
  - Hyponatremia
  - Hypocalcemia
  - Hyperphosphatemia
  - Hypermagnesemia
  - Acidosis/Alkalosis
  - Hypoglycemia
- Gastrointestinal (GI)—
  - Nausea, vomiting, diarrhea
  - GI hemorrhage, paralytic ileus
- Cardiovascular—
  - Fluid overload with water retention
  - Hypertension
  - Congestive cardiac failure
  - Pulmonary edema
  - Cardiac arrhythmias
  - Myocardial infarction
  - Pericarditis
- Hematologic—
  - Anemia
  - Platelet dysfunction
  - Bleeding from various sites
- Neurologic—
  - Neuromuscular irritability
  - Mental obtundation and coma
  - Seizures
- Multiple organ dysfunction
- Infections—
  - Sepsis
  - Pneumonia
  - Catheter-related infections
  - Urinary tract infections
  - Wound infections

Specific Treatment for Certain Specific Forms of Glomerulonephritis

Specific treatment for some forms of autoimmune glomerulonephritis, immune-complex disease and acute renal disease due to various forms of vasculitides includes the use of cytotoxic agents, corticosteroids, antiplatelet drugs and plasma exchange.

Use of Dialysis[20]

Dialysis enables homeostasis of fluid, electrolytes, acid-base and nitrogen balance, when this is difficult or impossible with the medical measures outlined above. Certain principles of management need to be stressed upon—

- The cause of ARF should as far as possible be determined and postrenal causes should be excluded before commencing dialysis.

- Attention should be given to preserving and maintaining a satisfactory hemodynamic state, so that renal perfusion is adequate.
- Sepsis should be vigorously treated.
- The dosage of all drugs administered to the patient are modified according to the degree of renal failure and the type of dialysis in use.
- Three types of dialysis (renal replacement therapy[21]) are available—
  - Intermittent hemodialysis.
  - Continuous hemofiltration/hemodiafiltration.
  - Peritoneal dialysis (intermittent or continuous).

They work on the principle of enabling water and solute clearance through a semipermeable membrane and discarding the waste products so produced. The mode of replacement therapy chosen for a particular patient depends on the nature and degree of homeostatic imbalance, the hemodynamic status and the background disease or complications present.

Indications for Dialysis

Fluid overload This is the most important indication for dialysis. When fluid overload produces increasing pulmonary congestion and edema, dialysis needs to be performed urgently.

In hemodynamically stable patients, intermittent hemodialysis provides the quickest method of removing fluid, 1–2 L/hour by ultrafiltration. In hemodynamically unstable patients peritoneal dialysis or continuous hemofiltration is safer and therefore preferable. The amount of fluid removed can be carefully titrated; generally 1–2 or more liters are removed over 24 hours and this can be repeated daily if necessary till fluid balance can be attained. Thus a large quantity of fluid can be removed over a few days. In continuous hemofiltration (CHF) the ultrafiltrate is isosmotic with plasma.

Electrolyte abnormalities Hyperkalemia is an important indication for dialysis, if it is marked, persistent or rapidly progressive. Rapid potassium removal is only possible by machine hemodialysis, the clearance rate of potassium being 100–200 mL/minute. Peritoneal dialysis or continuous hemofiltration does not allow a clearance rate of potassium greater than 20 mL/minute, and these forms of dialysis should be used to counter modest hyperkalemia or for maintaining potassium balance.

Toxic serum levels of calcium, magnesium and phosphates are also rapidly corrected by hemodialysis. Severe hypophosphatemia may complicate all forms of dialysis, if phosphates are absent in the diet or in the IV alimentation fluids.

Acid-base abnormalities Uremic acidosis and lactic acid acidosis can both be temporarily corrected by hemodialysis. Acidosis recurs quickly (particularly in patients with lactic acid acidosis) in the inter-dialysis period. Continuous arteriovenous hemofiltration provides continuous correction of acidosis, and is the treatment of choice in septic patients in ARF, who have both fluid overload and a lactic acid acidosis.

Uremic symptoms Dialysis is indicated with BUN levels higher than 100 mg/dL, particularly in the presence of uremic symptoms—pericarditis, encephalopathy, bleeding tendency, neuromuscular irritability and seizures.

The current practice is to initiate dialysis early rather than late in AKI. It is bad medicine to await serious complications of uremia before starting dialysis. *Most ICUs would consider dialysis when any one of the following is present—severe oliguria (<5 mL/kg per day), anuria for over 12 hours, pulmonary edema not responding to a diuretic, metabolic acidosis with a pH less than 7.2, uremic symptoms such as increasing obtundation or encephalopathy or pericarditis, or severe GI symptoms. The presence of any two of the above would be considered by most as a clear indication for dialysis.*

It must be however remembered that an over-aggressive approach to the very early commencement of dialysis in ARF does not necessarily equate with a reduction in mortality. In fact an over-aggressive approach in units that lack either experience or expertise can do more harm than good.

Intermittent hemodialysis may be necessary every other day or even daily, in hypercatabolic patients. Dialysis needs to be continued till recovery ensues. In ATN, this usually takes place within 2–8 weeks. Dialysis should be withheld if there is evidence of irreversible vital organ failure or severe irrecoverable cerebral damage.

Modes of Dialysis[22]

The mode of renal replacement therapy in an ICU for a given patient depends not only on the underlying medical problem but also on local resources, expertise and experience. We increasingly tend to use continuous hemofiltration/hemodiafiltration in preference to intermittent hemodialysis. Peritoneal dialysis is not indicated in the management of patients with ARF requiring dialysis, except in those where vascular access is unavailable or impossibly difficult. Continuous hemofiltration/hemodiafiltration offers the following advantages—

- Use of biocompatible membrane.
- Greater hemodynamic stability.
- Ability to control the quantum of removal of water over prolonged time.
- A leeway for increased fluid intake necessary both for hyperalimentation and for administering drugs intravenously.
- Prevention of both cerebral edema and increase in intracranial pressure.

A brief description of intermittent hemodialysis, peritoneal dialysis and continuous hemofiltration is given below. The techniques and the details regarding vascular access and performance of different forms of dialysis are best left to the nephrologist and trained nursing staff. The physician in the ICU must however be aware of the principles underlying the effectiveness, advantages and disadvantages of each form of

dialysis and the complications that can be encountered during dialysis in the ICU.

Hemodialysis

Advantages and Effectiveness

The major advantage of hemodialysis is its highly efficient solute removal, and its ability to remove fluid overload within a short period of time. Most modern dialyzers allow 150–200 mL/minute of urea clearance with blood flows between 200 mL/minute and 300 mL/minute. More rapid solute clearance can be obtained with newer filters when operated at a higher flow of 400 mL/minute. As much as 1–3 L of fluid can be removed per hour; fluid withdrawal is however limited by the patient's hemodynamic state. *A very rapid fluid withdrawal can produce disastrous consequences in critically ill patients*. Ordinarily a 4-hour hemodialysis should reduce pretreatment urea levels by about 50%.

Disadvantages

The major disadvantage is the rapidity of fluid withdrawal which is unsuitable in a hemodynamically unstable patient. The need for a large-bore vascular access and the need for anticoagulation are other disadvantages. The latter specially poses problems in patients who are actively bleeding.

Complications[23]

The following complications are often met with during or immediately after hemodialysis—

Hypotension Hypotension is related to poor tolerance of fluid removal. Poor tolerance to the acetate used in the dialysate fluid can potentiate hypotension. Fortunately, acetate is no longer used in the dialysate fluid. Bicarbonate based dialysates are always preferred in hemodynamically unstable patients and are now in universal use.

Hypotension resistant to volume replacement, together with respiratory distress, can in rare instances be due to relative bio-incompatibility between cuprophane and cellulose-based membranes. This has been dubbed the first use syndrome, and is treated with subcutaneous epinephrine and IV aminophylline. Definitive management consists in using more biocompatible materials.

Hypotension during dialysis should be treated by decreasing the blood flow, and administering a volume load with either colloids like albumin, or crystalloids like dextrose or normal saline.

Arrhythmias Cardiac arrhythmias are particularly prone to occur in hemodynamically unstable patients. Digitalis toxicity is another cause and is precipitated by the rapid lowering of serum potassium levels. Abnormalities in serum levels of magnesium and calcium, hypoxia and myocardial ischemia are other causes of cardiac arrhythmias. Cardiac arrest is a dreaded complication in critically ill patients. Arrhythmias should be promptly recognized and treated.

Hypoxemia Arterial hypoxemia can be due to two causes—

1. The loss of CO_2 through the dialyzer with subsequent diminishing of the respiratory drive. Oxygen administered through nasal prongs corrects the hypoxia.
2. The occurrence of the first-use syndrome due to activation of complement and of leukoagglutination within the lungs can cause severe bronchospasm with hypoxia. Dialysis needs to be promptly discontinued, and the bronchospasm should be countered by nebulization with duolin, IV hydrocortisone and if required by IV aminophylline.

Hemorrhage If serious hemorrhage occurs, previously administered heparin should be neutralized by protamine. One milligram of protamine ordinarily neutralizes 100 International Units of heparin. Protamine infusions should preferably be limited to a maximum of 15 mg over 5 minutes, to minimize the risk of anaphylactic reactions.

Dialysis disequilibrium syndrome This syndrome is characterized by headache, nausea, twitchings, mental obtundation, delirium and seizures, following rapid correction of severe uremia. Shorter duration of treatment to start with, using slower blood flow rates of less than 200 mL/minute, helps to minimize or prevent this syndrome.

Peritoneal Dialysis

The only indication for peritoneal dialysis (PD) is in patients with AKI in whom vascular access is difficult or impossible. In these patients, peritoneal dialysis remains the only alternative. Hemodynamically unstable patients can withstand peritoneal dialysis without further compromise of their circulatory system, as the rate of fluid removal is much slower than with hemodialysis.

The effectiveness of peritoneal dialysis is not as good as intermittent hemodialysis. Solute removal depends on the volume of the dialysate and dwell time within the peritoneal cavity. An aggressive schedule incorporates 2 L exchange every hour, providing 24 L of urea clearance per day. Less aggressive schedules involving 2 L exchanges every 4 hours, result in 8–10 L of urea clearance per day. Fluid removal depends on the concentration of glucose in the dialysate and the dwell time allowed. Higher concentrations of glucose (4.25% solutions) can provide a fluid removal of 500 mL/hour. A major advantage of this technique is that no anticoagulation is required. The method therefore is safer than hemodialysis in bleeding patients.

Severe fluid overload producing pulmonary edema is however best managed by intermittent dialysis or continuous arteriovenous hemofiltration.

Disadvantages and Complications[24]

- An important disadvantage and complication is impaired drainage. Problems can be particularly serious when the catheter allows unimpeded inflow, but the outflow is markedly reduced. This may be due to malpositioning

of the catheter or a ball-valve obstruction produced by omentum wrapped round the perforations in the catheter.

- Infection with resulting peritonitis is a serious complication. As opposed to peritonitis resulting from intrinsic disease, dialysis-induced peritonitis can be successfully managed by intraperitoneal antibiotics. When suspected, the WBCs in the effluent should be estimated. A WBC count greater than 100 granulocytes/μL points to infection. Gram stain of the effluent for organisms is also of help. A suitable antibiotic is added to the dialysate depending on the nature of infection present. The choice and dosage of antibiotics in the dialysate should be decided upon by the nephrologist. Gentamicin is preferred for Gram-negative infections, and vancomycin or cefazole for staphylococcal infections.
- Protein loss can be considerable in peritoneal dialysis.
- Compromised pulmonary function due to elevation of the diaphragm and hydrothorax is frequently observed. Peritoneal dialysis cannot be effectively used in breathless patients with pulmonary disease.
- Abnormal blood sugar levels and electrolyte disturbances may be induced during peritoneal dialysis.
- Peritoneal dialysis is very slow and ineffective in patients who are severely hypercatabolic, and who are in ARF, or when dangerous abnormalities in fluid and electrolyte balance need very prompt correction.

Continuous Hemofiltration

Continuous hemofiltration (CHF) is being increasingly used as the mode of dialysis in critically ill patients who have a large fluid overload, and in those who are hemodynamically unstable. It is also indicated when the use of IV alimentation necessitates the administration of large volumes of fluid.

In CHF, a highly permeable membrane acts as an artificial glomerulus by permitting hydrostatically driven ultrafiltration. The ultrafiltration leads to loss of water, solutes, urea and waste products in the ultrafiltrate. This method of solute clearance is termed convective clearance.

A large volume of fluid can be removed in a fluid-overloaded critically ill patient, without inducing hypotension or other circulatory disturbances because treatment lasts continuously throughout the day. The procedure can be carried out at the bedside and this is an added advantage. The need for an access to large vessels for excellent nursing and for continuous anticoagulation with heparin are the main drawbacks.

Continuous Arteriovenous Hemofiltration

This is perhaps the most commonly used mode of hemofiltration. In continuous arteriovenous hemofiltration (CAVH) blood is driven through the filter by the patient's own blood pressure, either via a large bore femoral artery cannula or via the arterial limb of an arteriovenous Scribner shunt. The blood traverses the biocompatible permeable filter, undergoes ultrafiltration and is returned to the circulation via a cannula in the femoral vein or via the venous limb of the Scribner shunt. Solute clearance and removal of nitrogenous waste products are not as efficient as in hemodialysis. Even so, significant and often adequate clearance of nitrogenous waste products is achieved because treatment is continuous throughout the day.

Continuous Arteriovenous Hemodiafiltration

Numerous modifications have been incorporated to improve solute clearance in the continuous arteriovenous hemodiafiltration (CAVHD) circuit. The most effective way of increasing solute clearance is to add dialysate flow countercurrent to the hemofiltration current. This can double solute clearance through diffusion of solutes. This technique is termed continuous arteriovenous hemodiafiltration.

Continuous Venovenous Hemofiltration and Hemodiafiltration

In continuous venovenous hemofiltration (CVVH), access to the circulation is obtained via a double lumen catheter inserted into the femoral or subclavian or internal jugular vein. Blood is pumped by a roller pump from the arterial limb of the double lumen catheter into the filter and after ultrafiltration and purification returns to the circulation via the venous limb of the double-lumen catheter.

If a counter-current diastolic flow is added to the CVVH current, solute clearance is further increased. This technique is termed continuous venovenous hemodiafiltration (CVVHD).

Large amount of fluid can be removed by the various techniques of continuous hemofiltration. A careful hourly measurement of fluid removed in relation to fluid replaced is mandatory and a frequent estimation of serum electrolytes is also necessary. Good nursing and constant attention are required for good results.

CLINICAL SYNDROMES ASSOCIATED WITH AKI

Pigment Nephropathy Due to Rhabdomyolysis or Acute Hemolysis[25] (Box 9)

Rhabdomyolysis is observed most frequently after severe traumatic crush injuries. In an intensive care setting it also occurs in patients with fulminant tetanus, acute polymyositis, acute myositis and rarely in severe leptospiral infections. Myoglobinuria with precipitation of myoglobin casts in renal tubules is the cause of acute renal injury and failure. Volume depletion from any cause (e.g. crush injuries) promotes precipitation of myoglobin within the tubules. Rhabdomyolysis is associated with painful muscles, and elevated creatinine kinase and aldolase levels in the blood.

Acute severe hemolysis in our part of the world is most frequently due to three causes—

1. The inadvertent administration of incompatible blood transfusion.
2. The use of certain drugs in patients who are G6PD deficient.
3. Acute hemolysis in falciparum malaria and black water fever.

Box 9: Important causes of rhabdomyolysis

- Exercise
- Tetanus
- Status epilepticus
- Trauma, crush injuries
- Heat stroke, hyperthermia
- Polymyositis, dermatomyositis
- Acute infective myositis
- Ischemia to the muscles of a limb
- Myopathies
- Drugs and toxins

Acute viral and *Salmonella* infections can also induce severe hemolysis in G6PD deficient patients with resulting acute renal shutdown. The presence of severe anemia, a high reticulocyte count, rise in serum bilirubin and a low haptoglobin are features of acute hemolysis. In the absence of detectable red blood cells on urinanalysis, a dipstick test positive for heme is diagnostic of myoglobinuria or hemoglobinuria. Patients with myoglobinuria and hemoglobinuria have dark brown and at times almost black urine. The serum in patients with myoglobinuria is clear, whilst in severe hemoglobinuria the spun serum sample is pink, free hemoglobin is detected in the serum and the serum enzymes particularly the lactate dehydrogenase (LDH) are raised.

Treatment

The most important step is to restore circulating volume quickly and to attempt a forced diuresis with mannitol 250 mL intravenously or furosemide 250–500 mg intravenously. Hydration with forced diuresis should aim for a urine output over 100 mL/hour. Alkalinization of the urine with IV sodium bicarbonate in patients with acute hemolysis may prevent precipitation of the heme pigment within the renal tubules.

Once oliguric renal failure has set in, it is unwise to persist with repeated use of mannitol or furosemide. Treatment is then continued on the lines mentioned earlier.

Hypocalcemia and severe hyperkalemia are frequent features of rhabdomyolysis and acute hemolysis.

Hepatorenal Syndrome[26]

This syndrome is characterized by renal failure with normal tubular function in a patient with chronic liver disease. It usually afflicts patients with alcoholic cirrhosis. Renal failure is related to increased preglomerular vascular resistance which leads to a reduced GFR, with diversion of blood flow away from the renal cortex. This occurs even in the presence of a normal or increased cardiac output. Oliguria, a low urine sodium concentration, a highly concentrated urine, a progressively increasing azotemia and the frequent presence of hyponatremia are characteristically observed. Renal failure in cirrhotic patients is precipitated by hemorrhage or paracentesis or diuretic therapy or following a slight fall in the intravascular volume following diarrhea. It can occur without any fall in arterial blood pressure.

Prevention is of crucial importance, as treatment of the fully evolved hepatorenal syndrome is of no avail. Hypovolemia should be prevented in cirrhotic patients, and if it does occur should be promptly treated. Treatment of hepatic failure is on the usual lines. Infection should be recognized and treated; nephrotoxic drugs such as aminoglycosides and NSAIDs should be stopped. Mannitol has been tried to expand intravascular volume, but is of little use and may result in intracellular acidosis. High doses of furosemide fail to act. Dialysis does not help and may in fact precipitate hypotension, shock and GI bleeding. In a fully evolved hepatorenal syndrome death is inevitable, and is preceded by hypotension, hyponatremia and mounting azotemia.

Syndromes with Pulmonary and Renal Involvement

A quickly evolving renal failure requiring intensive care occasionally occurs in association with a pulmonary pathology. Thus, pulmonary vasculitides are often associated with progressive renal failure. A classic example is Wegener's granulomatosis[27] associated with an arteriolitis within the kidneys or associated with a rapidly progressive glomerulonephritis. Other pulmonary vasculitides with renal involvement include the Churg-Strauss syndrome, polyarteritis nodosa and small vessel vasculitis. Autoimmune disorders which involve the lung and produce renal failure include systemic lupus erythematosus (SLE) and the Goodpasture's syndrome. Sepsis from any cause can result in acute lung injury and produce progressive renal dysfunction and failure. In the tropics, fulminant falciparum infection is an important cause of multiple organ dysfunction, with the CNS, the lungs and the kidneys bearing the brunt of the infection. A few poisons including organophosphorus poisons, the herbicide Paraquat can produce pulmonary edema and anuria due to ATN.[28]

Diagnosis is dependent on a careful consideration of the clinical features, radiological examination of the lungs, special diagnostic tests, a lung biopsy and in some instances a kidney biopsy. The antineutrophilic cytoplasmic antibody (ANCA) test is positive in Wegener's granulomatosis and in small vessel vasculitis. The anti-nuclear factor (ANF) and anti-DNA tests are positive in SLE. Immunofluorescent studies of material from kidney biopsy show IgG-immune complex deposits in SLE. The diagnosis of Goodpasture's syndrome can be made by detection of antiglomerular basement membrane antibodies in the serum. A kidney biopsy shows the presence of linear immunofluorescence in the glomerular basement membrane in Goodpasture's syndrome.

Treatment in acutely ill patients is difficult if a diagnosis is not established. ARF should be treated on lines mentioned earlier. Severe hemoptysis and progressive renal failure in Goodpasture's syndrome are treated with corticosteroids (pulsed doses of methylprednisolone, 15–20 mg/kg per day for 3 days, are used initially in critically ill patients), cyclophosphamide (1.5 mg/kg body weight) and plasmapheresis.

Acute renal failure occurring in severe forms of Wegener's granulomatosis and other forms of severe vasculitides is treated with corticosteroids and cyclophosphamide, as in the Goodpasture's syndrome.

Pulsed doses of methylprednisolone are used for rapidly evolving renal failure in SLE.

In poisonings involving the lungs and the kidneys, gastric lavage with the use of charcoal adsorbents is of use. Charcoal hemoperfusion and continuous arteriovenous hemofiltration may be tried in suitable cases.

Acute Kidney Injury in the Transplant Patient[29,30]

(Also see Chapter Critical Care of the Transplant Patient)

Renal failure may occur early in a transplant recipient—sometimes within 10 days of the transplant or late (after 10 days of the transplant). AKI progressing to ARF occurring early can be due to—

- Hyperacute immune rejection of the graft.
- ATN of the transplant.
- Problems related to surgery, e.g. obstruction, leak or infection.

Cyclosporine toxicity particularly in those receiving high IV doses of the drug presents with hypertension and prerenal azotemia; this should be differentiated from the other causes of ARF listed above.

Acute kidney injury progressing to ARF occurring in the late period after transplant may be due to acute immune rejection, renal artery stenosis, ureteric obstruction, infections, cyclosporine toxicity or recurrence of the original renal disease. Tacrolimus, an immunosuppressant often used after a renal transplant can also be a cause of acute renal injury. Blood levels of immunosuppressants in particular, cyclosporine and tacrolimus should be measured at periodic intervals. High blood levels are associated with increased nephrotoxicity.

Acute rejection of the transplant is diagnosed by the presence of tenderness and swelling over the transplanted kidney, fever, a fall in the urine output and increasing azotemia. Imaging studies and nuclear scans help in distinguishing between the different causes of ARF in a transplant patient. At times, a kidney biopsy may be necessary to reach a definitive diagnosis.

Management is specialized, and should be in consultation with a nephrologist and the transplant surgeon.

Critical Illnesses in Patients on Chronic Dialysis

Patients on maintenance dialysis are often admitted to a critical care unit for an acute illness. The following problems are frequently encountered—

Acute Hypertension

This is often caused by an increased ingestion of salt and water by the patient in the interdialysis period. Acute left ventricular failure and hypertensive encephalopathy may occur. These complications mandate admission to an ICU and appropriate treatment. Pulmonary edema is generally unresponsive to diuretic therapy and requires removal of the extra fluid by dialysis.

Acute Hypotension and Arrhythmias

Acute hypotension, arrhythmias and even cardiac arrest may occur at times during or immediately after hemodialysis, necessitating emergency transfer to the ICU. If the patient is hypotensive, he should be given a volume load. A brady rhythm is countered by IV atropine 0.5–1 mg. Sudden atrial fibrillation with a very rapid ventricular rate needs IV amiodarone (see Chapter Tachyarrhythmias in the Intensive Care Unit).

Upper Gastrointestinal Bleeds

These are extremely common; antacids containing magnesium are best avoided and the dose of H_2 blockers may need to be adjusted.

Electrolyte Disturbances

Occasionally, a patient is admitted for acute hyperkalemia or acute acidosis (see Sections Fluid and Electrolyte Disturbances in the Critically Ill Patient). Hyperkalemia can pose a serious life-threatening emergency, requiring prompt recognition and treatment.

Acute Hypoglycemia

This is observed at times in patients with chronic renal failure. Sudden drowsiness, mental obtundation, abnormal behavior, unconsciousness, generalized seizures or even focal neurological signs should alert the clinician to this possibility. We have observed recurrence of hypoglycemia after the discontinuation of IV dextrose. An increased incidence of hypoglycemia observed in our patients may perhaps be related to the fact that glucose is not used in the dialysate fluid, and that glucose may be lost from the blood during dialysis with resultant hypoglycemia. This is more frequently observed in diabetics on insulin.

Use of Acetate in the Dialysis Fluid

Acetate is no longer used in the dialysate fluid. In early years when it was used, life-threatening clinical features during or immediately after hemodialysis were sometimes observed. The patient became increasingly breathless due to severe acidosis; hypotension, arrhythmias and cardiac instability were also observed. The problem now does not occur as acetate has been replaced by bicarbonate in the dialysate fluid.

Acute Infections

Patients in chronic renal failure on maintenance dialysis are immunosuppressed and are prone to infections (see Section The Immunocompromised Patient). Antibiotics have more prolonged therapeutic levels in these patients, and nephrotoxicity of antibiotics and other drugs is not of major importance in these patients.

Infection of the vascular access is common in patients on hemodialysis. Though pain, local erythema and tenderness are common over the access site, physical signs may be minimal. Systemic sepsis following bacteremia may originate from an apparently noninfected site of vascular access. This should always be kept in mind in patients with systemic

infection. Successful treatment of infection of the access site is generally possible with prolonged administration of antibiotics. Antibiotic regimes for such infections generally include vancomycin, since this drug is poorly dialysable and a single dose results in adequate serum levels for 7 days.

Thrombosis of a Vascular Access Site

Thrombosis of a vascular access site is another complication observed in critically ill patients who are on chronic dialysis. At times a prolonged period of hypotension results in thrombosis. At other times, infection at the site or venipunctures at or near the site leads to thrombosis. Venipunctures should always be done on the contralateral arm and avoided on the arm which has a graft or a surgically fashioned fistula. If an access site is found to be thrombosed (absent thrill or bruit), immediate surgical consultation is necessary. Thrombolytic therapy with IV urokinase may at times obviate the need for surgical treatment.

Fluid and Electrolyte Restriction in Patients on Chronic Hemodialysis

Fluids should be restricted from 700 mL to a maximum of 1 L. The degree of fluid restriction is dictated by the tendency of the patient to develop hypertension or pulmonary edema during the interdialysis period.

Nutritional Requirements

Once on dialysis, the patient is encouraged to eat well. Protein requirements are about 1 g/kg per day. In an average adult, total caloric requirement is about 2,000 calories per day or 35 kcal/kg per day.

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CHAPTER 54

Critical Care in Acute Hepatic Failure

INTRODUCTION

Acute hepatic failure (AHF) is the clinical syndrome produced by sudden and severe liver cell dysfunction in a previously healthy individual. It is characterized chiefly by hepatic encephalopathy and coagulopathy. Severe loss of liver cell function sets into motion a downward spiraling multiorgan dysfunction syndrome that culminates fatally. Death can occur even when the liver has begun to recover. Hepatotropic viruses are the most common cause of acute hepatic failure in India and Southeast Asia, whereas in the West (the UK, the USA) the most common cause of AHF is acetaminophen toxicity. AHF has a high mortality and treatment is largely supportive. Liver transplantation is the only proven and definitive option for patients who are not likely to recover. AHF accounts for 5–6% of liver transplants. Many patients die before a suitable organ can be identified.

Critical care is mandatory in a patient with sudden severe liver cell dysfunction. Critical care is also often necessary in patients with chronic liver disease (as in cirrhosis), who develop acute encephalopathy or a severe gastrointestinal (GI) bleed, or a complicating infection, or who become oliguric or azotemic.

The term fulminant hepatic failure (FHF) and acute hepatic failure (AHF) are often used interchangeably. AHF is defined as the presence of severe hepatic dysfunction and the presence of encephalopathy (regardless of grade) and coagulopathy [internationalized normalized ratio (INR) >1.5] within 8 weeks of the appearance of symptoms in patients with no previous history of underlying liver disease. The above was the original definition of AHF proposed in 1970s by Trey and Davidson. Since then other different classifications have emerged (Box 1).[1-3]

Box 1: Various classifications of acute hepatic failure

- *Trey and Davidson*[1]—
  - Fulminant hepatic failure: development of HE and coagulopathy within 8 weeks of onset of symptoms
- *British classification*[3]—
  - Acute liver failure (includes only patients with encephalopathy)
  - Subclassification depending on the interval between jaundice and HE—
    - » Hyperacute liver failure: 0–7 days
    - » Acute liver failure: –28 days
    - » Subacute liver failure: 29–72 days
    - » Late-onset acute liver failure: 56–182 days
- French classification—
  - Acute hepatic failure: a rapidly developing impairment of liver function
  - Severe acute hepatic failure: prothrombin time or factor V concentration below 50% of normal with or without HE
- Subclassification—
  - Acute hepatic failure: HE within 2 weeks of onset of jaundice
  - Subfulminant hepatic failure: HE between 3 and 12 weeks of onset of jaundice

Abbreviation: HE, hepatic encephalopathy.

The interval between the appearance of hepatic encephalopathy (HE) and jaundice forms the basis of these classifications, allowing grouping of patients with regard to similar causes, clinical features and prognosis.

What was the basis of the British and French Classification formulated after that of Trey and Davidson? These subsequent

Box 2: Recommendation of International Association for the Study of the Liver (IASL) Subcommittee for the definition and classification of AHF and SHF

Nomenclature—
- AHF: occurrence of HE within 4 weeks after onset of symptoms
- SHF: development of ascites and/or HE from 5 weeks to 24 weeks after onset of symptoms

Diagnostic criteria of liver failure—
- AHF: Encephalopathy
- SHF: Encephalopathy and/or progressive ascites

Maximum interval between onset of icterus and features of liver failure—
- AHF <4 weeks
- SHF >4–24 weeks

Subclassification—
- Etiological to indicate specific cause of AHF
- Temporal to indicate the rapidity of encephalopathy—
  - Hyperacute—Encephalopathy within 10 days of icterus.
  - Fulminant—Encephalopathy between 10 days and 30 days of the onset of jaundice
- Not otherwise specified

Abbreviations: AHF, acute hepatic failure; SHF, subacute hepatic failure; HE, hepatic encephalopathy.

classifications were based on the observation that in the West patients with AHF who developed encephalopathy within a week to 10 days of the onset of jaundice had significantly higher survival rates than similar patients who had encephalopathy after 1 week or 10 days of the onset of jaundice. This observation influenced the selection of patients with AHF for liver transplantation.[4]

In contrast to this observation, an important study in India[5,6] showed that in India patients with AHF presented with encephalopathy within 3 weeks of the onset of jaundice and 4 weeks after the onset of symptoms and that the rapidity of the onset of the encephalopathy did not influence survival.[7] In this study when liver failure occurred more than 4 weeks after the onset of an acute hepatic illness, the presentation was that of progressive ascites; encephalopathy was an extremely rare presenting feature at this stage. These patients had subacute hepatic failure (SHF), with the majority dying within a period of 6 months. Similar patients have been described in the West as having late onset hepatic failure (LOHF). To resolve geographical differences with regards to definition, sub-classification, the International Association for the Study of the Liver (IASL) has recommended a new set of definitions and subclassification of AHF and SHF (Box 2).

ETIOLOGY

World wide, viral hepatitis is the most common cause of AHF. Viruses A, B, C, D, E, can each produce fulminant hepatitis. The proportion of fulminant cases (AHF) due to each of the major viruses A, B, C, E varies with the geographical area under study. All published reports from the Indian subcontinent have identified hepatitis viruses as the etiological agent in 95–100% of patients with AHF.[5,8,9] The same holds true for all Eastern countries, in particular for developing countries. Patients with AHF in India and Eastern countries therefore constitute by and large a homogenous group, since other etiological factors (i.e. nonviral factors) are infrequently observed. This is in contrast to Western countries where patients with AHF form a more heterogeneous group, since besides hepatic viruses, other etiological factors are also observed. The reason for this difference is chiefly the marked endemicity of hepatic viruses in the East. Hepatitis A and E viruses are endemic in India and other Eastern countries. There are about 40 million Hepatitis B virus (HBV) and 10 million Hepatitis C virus (HCV) carriers in India.[10,11]

The most common hepatitis virus causing AHF in the Indian subcontinent and in the developing eastern countries and Africa is Hepatitis E, the virus being responsible for 23–41% of patients with AHF. Hepatitis B is the next most important cause of AHF in India, being responsible for 11–27% of such cases.[12] Hepatitis E virus is very rare in the West but Hepatitis B has been incriminated as the most important hepatic virus causing AHF in the West and in Australia.[13,14] Hepatitis A virus is responsible for 2–8% of patients with AHF both in the East and West.

Hepatitis C virus is reported to cause AHF in a little over 4% of patients in India.[5] However, reports from Japan and Taiwan have implicated Hepatitis C as the etiological agent in 50% of patients with non-A non-B AHF.

Hepatic B can cause AHF through several mechanisms—
- Primary hepatitis B infection.
- Reactivation of hepatitis B in patients with chronic hepatitis B virus infection.
- Superinfection with hepatitis D virus or other hepatic viruses.
- Infection with hepatitis B mutants.
- Occult or cryptic hepatitis B infection.

Primary hepatitis B virus infection can be missed because a number of patients have negative serum hepatitis B surface antigen (HBsAg) and serum HBV-deoxyribonucleic acid (DNA). Acute HBV infection is diagnosed notwithstanding the above by the presence of IgM antibodies to hepatitis B core antigen. Absence or low level of HBsAg and HBV-DNA in primary hepatitis B infection is associated with a better prognosis and a lower rate of recurrence after orthotropic liver transplantation.
- *AHF after reactivation of hepatitis B virus* is chiefly seen in immunocompromised patients. This form of the disease manifests in a subfulminant form and has a poor prognosis.
- *Coinfection with HBV and hepatitis D virus (HDV) or superinfection by HDV* can also lead to AHF. AHF has been also observed in 2.5–6% patients infected with virus D. The diagnosis of HDV is made by the presence of HDV antigen, IgM antibodies to HDV and the detection of HDV-ribonucleic acid (RNA).

Box 3: Important drugs causing AHF

- Isoniazid
- Valproate
- Halothane
- Phenytoin
- Sulfonamides
- Propylthiouracil
- Amiodarone
- Disulfiram
- Dapsone
- Bromfenac
- Troglitazone
- Zidovudine
- Lamivudine
- Lamotrigine
- Gatifloxacin
- Methotrexate

Abbreviation: AHF, acute hepatic failure.

Box 4: Causes of AHF

- Viral Hepatitides—Hepatitis A, B, C, D, E, G—
  Other viruses—
  - Human herpesvirus
  - Cytomegalovirus
  - Epstein-Barr virus
  - Dengue virus
  - Herpes simplex virus
  - Varicella-zoster virus
  - Paramyxovirus
  - Parvovirus B19
  - Adenovirus
  - Yellow fever virus
- Drugs (see Box 3)
- Other infections—
  - Leptospiral
  - *P. falciparum*
  - Disseminated tuberculosis
- Vascular—
  - Ischemic
  - Veno-occlusive disease
  - Budd-Chiari syndrome
- Malignancy—
  - Malignant infiltration
  - Non-Hodgkin's lymphomas
- Miscellaneous—
  - Wilson's disease
  - Autoimmune hepatitis
  - Acute fatty liver of pregnancy
  - Reye's syndrome

- *Hepatitis B virus mutants* A number of patients with AHF show no positive serological markers. Mutations in the hepatitis B core region could result in the production of Hepatitis Bc antibodies that may not be detected by the usual enzyme-linked immunosorbent assay (ELISA) kits supplied today.
- *Occult or Cryptic Hepatitis B virus infection* These patients with AHF though negative for HBsAg and anti HBc IgM, have HBV-DNA detectable by polymerase chain reaction (PCR) studies either in the serum or liver tissues.[15-17] The incidence of occult or cryptic infection is low, except in Japan where the reported incidence is as high as 50%.[15]

Other viruses in rare instances have been reported to cause fatal hepatic necrosis, particularly in immunocompromised patients. The more commonly implicated viruses are cytomegalovirus (CMV), human herpes virus- 6 (HHV-6), Epstein-Barr virus (EBV), herpes simplex virus (HSV), hepatitis G virus.[18,19]

In Africa and other endemic tropical countries the yellow fever virus is to be always kept in mind as a cause of AHF.

In India and other tropical countries, AHF can be due to leptospiral infection and rarely due to fulminant *Plasmodium falciparum* infection as well.

After viral infections, idiosyncratic drug reactions are the most common cause of AHF in India. Drug induced liver damage is also a significant cause of death in patients with AHF in Western countries. The most frequently incriminated drugs in India are isoniazid, in particular isoniazid administered in conjunction with rifamipicin, antibiotics, nonsteroidal anti-inflammatory drugs, antidepressants, herbal or dietary supplements and immunomodulating agents (Box 3).[20] Dose, duration, hepatic metabolism of the drug may all be important in the development of drug-induced liver cell injury.

Poisonings causing AHF are rare in our country. In contrast paracetamol poisoning (with suicidal intent) is the most frequent and most important cause of AHF in the West—particularly in the United Kingdom (60%), USA and Europe (15–20%). Acetaminophen overdose accounts for 30–35% of AHF in the United States. Besides the use of the drug with suicidal intent, overdose of the drug over several days with intent to relieve pain or high fever can also cause poisoning resulting in AHF. Doses not considered toxic (<4g/day in adult, <8 mg/day in infants), might cause hepatotoxicity if other comorbid factors exist, such as alcohol ingestion, fasting, malnutrition, underlying chronic hepatic disease. Hepatic toxicity in paracetamol poisoning reaches a maximum 1 or 2 days after the overdose and the rise in liver enzymes together with a rise in INR reach their peak on the 3rd day. A continued rise in INR after the 3rd day is associated with 90% mortality. The peculiarity in liver dysfunction observed with acetaminophen poisoning is the comparatively very modest rise in bilirubin in contrast to the very high level of the liver enzymes and the high INR (Box 4).

In India, phosphorous poisoning in children due to the ingestion of fire crackers containing phosphorus, and a combination of phosphorus and arsenic poisoning due to ingestion of rat poison (suicidal attempt) are rare but important causes. Ingestion of wild poisonous mushrooms is one other rare cause of AHF. Industrial poisons and solvents can cause AHF, but these are rarely encountered.

In an intensive care setting progressive liver cell failure is at times seen in patients with cardiac disease and a very low cardiac output. This is due to ischemia to the liver perhaps combined with severe hepatic venous congestion.

Severe shock from any cause can also result in ischemic liver injury and failure. The prognosis remains good if the primary cause of shock can be corrected. The association of severe sepsis causing shock with AHF worsens the prognosis.

Acute fatty infiltration of the liver in full term pregnant women and eclampsia may also present with AHF. Acute Wilson's disease should always be excluded in patients less than 40 years old, particularly in the presence of hemolysis and when all viral markers are negative. Acute autoimmune hepatitis can also cause FHF and the diagnosis may be impossibly difficult if auto-antibodies are negative.

Budd-Chiari syndrome, veno-occlusive disease are other rare causes of AHF; they carry a dismal prognosis. Other causes of AHF are non-Hodgkin's lymphoma, involving the liver and extensive malignant metastasis involving the liver. Reye's syndrome is only rarely observed in the pediatric population since the use of aspirin has been curtailed in children. Finally, we have seen AHF rarely in patients with disseminated hematogenous tuberculosis massively involving the liver.

Miscellaneous cardiovascular, vascular, metabolic and other disorders stated above are responsible for 2–10% of patients with AHF.

In 10–12% of patients with AHF no cause can be detected in spite of a meticulous search. These are termed cryptogenic AHF. The possibility that AHF in these patients could be due to undetected Hepatitis B mutants, to occult or cryptic Hepatitis B infection, or to new hepatitis viruses as yet undiscovered, must be kept in mind.

CLINICAL FEATURES

The illness typically starts with nonspecific symptoms such as malaise, nausea, vomiting in a previously healthy individual. Abdominal pain may occur particularly in children; it may be acute and first felt in the right iliac fossa. Occasionally an appendectomy is performed with disastrous postoperative sequelae. These nonspecific symptoms are quickly followed by jaundice, rapid onset of an altered mental state that can progress to increasing obtundation and coma. Jaundice, an altered mental state and a coagulopathy characterized by a prolonged prothrombin time or an increased INR are the hallmarks of AHF. Fetor hepaticus is generally present. The liver to start with is palpably enlarged and tender but as the disease progresses it shrinks so that it is no longer palpable. The liver dullness on percussion is also progressively reduced. The constellation of the above mentioned clinical features are distinct from those observed in patients with chronic hepatic insufficiency regardless of the etiology.

Important laboratory features include a rise in serum bilirubin, high levels of liver enzymes, a lowered blood sugar, respiratory alkalosis and/or metabolic acidosis.

If the patient recovers the serum bilirubin starts to fall and the INR gradually normalizes. Clinically, the state of altered consciousness improves. If the disease progresses, the bilirubin level continues to rise and the INR also continues to increase. The degree of rise in liver enzymes is not a guide to prognosis, nor does a fall in liver enzymes necessarily indicate recovery. In fact the liver enzymes often fall with worsening disease, reflecting severe hepatic necrosis, with few liver cells alive to produce enzymes.

The course of AHF is beset with numerous complications. These include cerebral edema, renal failure, pancreatitis, acute respiratory distress syndrome (ARDS), cardiorespiratory failure and a coagulopathy that can lead to hemorrhagic complications. Supervening sepsis is frequently observed. The overall feature is that of multiple organ failure, not a single organ system being spared. Death can occur from any one of these complications but is most frequently due to cerebral edema or to supervening infection.

The following section to start with describes hepatic encephalopathy which is the hallmark of AHF. It then goes on to briefly discuss the other important complications observed in AHF.

Hepatic Encephalopathy

Encephalopathy is an essential clinical feature of AHF, distinguishing AHF from acute severe hepatitis. The time of onset of encephalopathy after the appearance of jaundice distinguishes AHF from subacute fulminant hepatic failure (SAHF).

The neuropsychiatric manifestations that characterize encephalopathy are often sudden in onset and rarely may precede the occurrence of clinical jaundice. Excitability, delusions, nightmares, drowsiness alternating with a markedly hyperkinetic state may be observed. At times, the excitability can be manic in nature. Spontaneous seizures may occur. The slightest stimulation (as an attempt to examine the patient) may provoke shouting and violent behavior. Flapping tremors may be observed to start with, but disappear with increasing obtundation. If the disease progresses, deep coma eventually results, the patient being unresponsive to all painful stimuli.

Disturbances in the conscious state should be charted and the encephalopathy graded as follow—

- Grade 1⟶Confused, altered mood or behavior with psychometric deficit.
- Grade 2⟶Drowsy, increasing behavioral changes.
- Grade 3⟶Stuporose, confused, incoherent but still obeying simple commands.
- Grade 4⟶Coma—cannot be aroused.

The prognosis in patients with Grade 1 and Grade 2 encephalopathy is good, whereas the prognosis in Grade 3 and Grade 4 encephalopathy is very poor.

The pathophysiology of hepatic encephalopathy is unclear and is probably multifactorial. Elevated ammonia

levels and increased ammonia within the brain[21,22] play an important role. Additional factors leading to encephalopathy include elevated levels of short chain fatty acids, false neurotransmitters, benzodiazepines and γ-aminobutyric acid. The electroencephalography (EEG) typically shows high amplitude wave forms at 5–7 cycles per second pointing to diffuse slowing of cortical activity. Subclinical seizure activity is often present, emphasizing the importance of EEG monitoring.

Seizure activity has been related to an excessive build-up of glutamine within the central nervous system (CNS). Glutamine synthesized within the cells is transported into the mitochondria where it is metabolized by glutaminase to glutamine and ammonia. The progressive increase in ammonia within the mitochondria leads to an increase in their permeability and to oxidative damage of mitochondrial constituents. Glutamine is therefore considered to be the "Trojan Horse" that allows a build-up of ammonia within the cell mitochondria.[23] The glutamine derived within the mitochondria causes swelling of astrocytes leading to disturbed function.

Cerebral Edema

Cerebral edema is often the most common immediate cause of death in AHF. It is caused by several possible contributing factors.[24,25] These include—

- Cerebral hyperemia.
- Disruption of the blood brain barrier resulting in vasogenic edema.
- Cytotoxic effects of ammonia, glutamine and other amino acids.
- The effects of proinflammatory cytokines.
- Loss of autoregulation of cerebral blood flow, related to a dysfunction of the sodium potassium ATPase pump.

Patients with AHF often develop relative or absolute cerebral hyperemia because perfusion is not well matched to the reduced cerebral metabolic rate. Indicators of the above are either a decrease in the transcranial oxygen content difference (arterial oxygen content—jugular bulb oxygen content) to less than 4 mL/dL or an increase in the systolic blood flow velocity in the middle cerebral artery. Serial transcranial Doppler ultrasonographic recordings of cerebral blood flow velocity help detect hyperperfusion or hypoperfusion which suggest impaired cerebral autoregulation.[26] Cerebral ischemia and neurological damage can occur if the cerebral perfusion pressure (mean systemic arterial pressure–intracranial pressure) is not maintained above 40–50 mm Hg.

Increasing cerebral edema leads to brainstem dysfunction. The clinical features of cerebral edema and brainstem dysfunction include deepening disturbance in conscious state, systolic hypertension, hyperventilation, myoclonic jerks, convulsions, dysconjugate eye movements, skew deviation of eyes and decerebrate rigidity. Decerebrate posturing can occur spontaneously or on stimulation. Plantars are generally flexor but an extensor response may occur. Depressed brainstem function ultimately leads to absent dolls eye movements, and absent vestibulo-ocular reflexes. The pupils are dilated and react sluggishly. A loss of pupillary reflex is terminal. Ultimately increasing edema leads to brainstem or uncal herniation and death.

Coagulopathy

The coagulopathy in AHF is due to inadequate production of coagulation factors. There is a decrease in levels of factors II, IV, VII, IX and X with a prolongation of prothrombin time (an increase in INR) and activated partial thromboplastin time (APTT). An imbalance between procoagulant and anticoagulant factors can lead to excessive thrombosis in the smaller vessels of various organ systems or to the picture of disseminated intravascular coagulopathy (DIC). AHF also often causes enhanced fibrinolytic activity. The combination of deficient clotting factors and enhanced fibrinolytic activity leads to bleeding—from injection sites, from the GI tract, from body orifices and into organ systems. Bleeding is often worsened by the frequent presence of thrombocytopenia (<50,000/mm^3) and by impaired platelet function.

Hypoglycemia is common with worsening liver cell function. Drowsiness and other features of hypoglycemia if unrecognized are mistaken for increasing severity of hepatic encephalopathy. Hypoglycemia is due to depletion of glycogen stores and impaired neoglucogenesis; it may be refractory to the infusion of intravenous dextrose.

Other metabolic complications include metabolic acidosis, hyponatremia, hypokalemia, hypophosphatemia, and lactic acid acidosis.

Renal Failure

Acute renal failure is observed in 30–70% of patients. It is multifactorial in etiology—hypovolemia, sepsis, DIC and the use of nephrotoxic drugs are all contributory factors.

Cardiorespiratory Failure

Persistent hypotension, arrhythmias point to cardiac dysfunction, while increasing tachypnea with a partial pressure of oxygen in the blood (PaO_2) less than 60 mm Hg point to respiratory failure. The occurrence of ARDS is an ominous complication.

Gastrointestinal dysfunction includes gastric dilatation, ileus, colonic distension, GI bleed. Acute hemorrhagic necrotizing pancreatitis is a well known complication that hastens the end.

Sepsis

Supervening nosocomial infection is of frequent occurrence in patients with Grade 3, Grade 4 encephalopathy. Infections can be due to Gram-negative or Gram-positive organisms or due to fungal infections. Infections hasten the end and add to the severity of the multiorgan dysfunction syndrome. In one prospective study of 50 patients, 80% had culture positive infection and in half of the remaining patients, infection was suspected but cultures were negative.[27]

Box 5: Diagnostic evaluation of AHF

- History, including history of drugs and possible poisons ingested; clinical examination
- Hematological—Hb, platelet count, CBC, blood group, bleeding time, prothrombin time, quantitative estimation of clotting factors
- Biochemical—Blood glucose, serum bilirubin, AST, ALT, serum proteins, blood urea, serum phosphates, serum electrolytes, serum calcium, serum magnesium, serum amylase
- Microbiology—Hepatitis B antigen and IgM anticore antibody, antiserum delta, hepatitis A (IgM) antibody, Hepatitis C (IgM) antibody, Hepatitis C DNA, blood, sputum, urine cultures; smear for malarial parasites, IgM for leptospiral antigen
- Arterial Blood Gas Analysis—Arterial pH and arterial blood gas measurements
- Others—ECG, X-ray of chest and abdomen, ultrasound of the abdomen, EEG
- PCR tests for other hepatitis producing viruses—notably CMV, EBV, herpes group of viruses
- A toxicology screen, e.g. acetaminophen blood levels
- In special cases—autoimmune markers—ANA, ASMA
- Serum ceruloplasmin levels, if Wilson's disease is suspected

Abbreviations: CBC, complete blood count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; ECG, electrocardiography; EEG, electroencephalography; PCR, polymerase chain reaction; CMV, cytomegalovirus; EBV, epstein-barr virus; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibody.

The syndrome of AHF is thus characterized by severe progressive multiple organ dysfunction. Amazingly, if recovery of liver function occurs, complete recovery ensues.

INVESTIGATIONS (BOX 5)

The grading of encephalopathy, and intake-output charts should be carefully maintained.

Biochemical investigations should include serum bilirubin, serum transaminases [Aspartate aminotransferase (AST), Alanine aminotransferase (ALT)], serum alkaline phosphatase, and serum proteins with the albumin:globulin ratio. The serum transaminases though high to start with, fall with worsening liver function, as there is less viable liver tissue left. The prothrombin time (PT) is extremely useful both for gauging the degree of liver cell dysfunction, and as a prognostic guide. A PT more than double the control carries a bad prognosis. The blood ammonia level is frequently raised in HE and coma. Serum electrolytes, Ca, P, Mg, urea, creatinine, glucose and serum amylase should also be done; biochemical tests should be repeated as and when necessary. Arterial pH and blood gas estimation is important.

Hematological investigations include hemoglobin estimation, blood and platelet count, and blood group. Relevant tests for clotting factor disturbances and DIC are also done.

Microbiological tests include viral markers for hepatitis A, B, C, D and E. These include tests for hepatitis B surface antigen, IgM anticore antibody, serum antidelta, hepatitis A IgM antibody, hepatitis C IgM antibody, hepatitis D IgM antibody and hepatitis E IgM antibody. Hepatitis C antibodies may be absent as they may take some weeks to be detected. Hepatitis C RNA by the PCR should therefore be done. It has already been pointed out that in fulminant hepatitis due to virus B infection the hepatitis B surface antigen may be cleared and therefore negative. The IgM antibody to the core antigen should always be done to prove the diagnosis. Serum HBV DNA is usually negative. Rapid viral clearance indicates a good immune response and perhaps a better prognosis. The possibility of Hepatitis B mutants or cryptic Hepatitis B infection should be kept in mind.

In tropical countries, a smear for *P. falciparum* infection, and serology for leptospiral infection should always be done.

Where the etiology remains unclear, serology and PCR tests for other hepatitis producing viruses (listed under etiology) should be performed—notably cytomegalovirus (CMV), EBV, herpes group of viruses. Few hospitals in our country have facilities and expertise to perform these tests.

A toxicology screen needs to be done in suspected poisoning; this includes an acetaminophen blood level if overdosage with the drug is thought possible.

When the usual viral markers for hepatitis are negative, autoimmune markers—antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA) should be done. Serum ceruloplasmin levels become necessary if Wilson's disease is being considered (e.g. in patients less than 40 years without any explanation for AHF).

Blood cultures are necessary, particularly if secondary infection is suspected. Similarly, cultures of urine, sputum or other body secretions should be done and repeated as and when necessary. Electrocardiography (ECG), X-ray chest, ultrasonography (USG) of the abdomen to monitor liver size, are necessary. Imaging studies of the head are generally of not much use, other than to detect an intracranial bleed. Cerebral edema is not necessarily detected on computed tomography (CT) or magnetic resonance imaging (MRI).

If available, a portable EEG is useful to gauge the degree of hepatic encephalopathy. Increasing unconsciousness is characterized by increasing amplitude and decreasing frequency of the EEG tracings. Triphasic waves are observed in deep coma; these waves are only observed in patients over 20 years of age, and are of ominous significance. Decreasing amplitude of the EEG tracing is observed in terminal cases; finally there is a total absence of rhythmic activity.

DIAGNOSIS

Diagnosis is generally easy. An early mistake is to suspect an acute abdomen when the onset is characterized by nonspecific symptoms, fever, vomiting and acute abdominal pain. Even when icterus is absent these patients invariably demonstrate a rise in the serum transaminases.

Neuropsychiatric manifestations of HE occasionally may precede a rise in serum bilirubin. We have witnessed a diagnosis of acute mania (for which psychotropic drugs were administered) in a patient with hepatic encephalopathy who died from AHF due to virus A infection within 4 days of the illness.

In areas endemic to *P. falciparum* infection, particularly when the patient has high fever, blood smear examination for malarial parasites should always be done.

In patients with severe muscle pain, conjunctival injection and urinary findings suggestive of glomerulonephritis, leptospiral infection should be kept in mind. The dengue virus is also reported occasionally to produce extensive hepatic necrosis. The blood tests are positive for both dengue antigen and IgM antibodies to the virus.

Immunocomprised patients are susceptible to uncommon viral infections (cytomegalovirus, herpes virus in particular) that may cause fulminant hepatitis.

MANAGEMENT

Intensive care is mandatory in AHF. It is best to admit the patient to a good intensive care unit (ICU) as soon as definitive neuropsychiatric features become evident. It is wrong to avail of intensive care facilities only when the patient is comatose, as critical care in the early phases may prevent the evolution into deep coma in some patients with severe hepatic necrosis. Even though the survival rate in a good ICU setting has improved, the mortality is still forbiddingly high. Once in ICU the physicians should get in touch with a liver transplant unit for a possible hepatic transplant. In fact ideally, any patient with acute liver disease should be treated in an ICU within a liver transplant center or transferred to an ICU in a liver transplant center as quickly as possible. This is well-nigh impossible in Mumbai as there is no transplant unit that can take on this responsibility. Transfer to Delhi and Chennai (where liver transplant centers are present) is difficult for very ill patients. Also there is a great scarcity of cadaver liver transplants in India, rendering successful liver transplantation in AHF in our country (outside cities with good transplant centers) a remote possibility.

A short summary of the management protocol is given in Box 6.

Box 6: Management of acute hepatic failure

- Overall critical care—
  - Nasogastric tube
  - Central venous line for administration of IV fluids and monitoring of CVP
  - Self-retaining catheter for monitoring of urine output
  - Monitoring of temperature, pulse, BP, CVP, ECG, intake-output charts
- Maintain fluid, electrolyte and acid-base balance
- Management of hepatic encephalopathy—
  - Avoid sedation or diuretics
  - Stop protein feeds
  - Amoxycillin 500 mg qds + metronidazole 400 mg thrice daily given through nasogastric tube
  - Lactulose 10–30 mL 8 hourly orally
  - Daily large bowel wash or enema
- Reduce cerebral edema with IV mannitol
- Treat hypoglycemia using continuous IV infusion of 10–20% dextrose
- Management of bleeding tendencies—
  - Transfusion of packed RBCs, fresh frozen plasma, cryoprecipitate, Vitamin K, specific deficient clotting factors as required
- Maintenance of nutrition—stop or sharply reduce proteins
- Give carbohydrates, strained vegetable soup, IV 20% dextrose, Vitamins B and C and multivitamins
- Correct hypoalbuminemia with IV salt-free albumin infusions
- Support other organ systems
- Control of infection
- Diagnose and treat complications
- Consider (when facilities available) a liver transplant in selected cases

Abbreviations: IV, intravenous; BP, blood pressure; ECG, electrocardiography; CVP, central venous pressure.

General Measures

The patient is barrier-nursed in the ICU; special care, with nurses and attendants using masks and gowns, is necessary. Patients with fulminant virus B hepatitis should be nursed by staff vaccinated against the HBV.

In a drowsy patient, or in a patient with a disturbed sensorium, the following general measures are promptly implemented—

- A nasogastric tube is passed and the stomach deflated. Vigorous suction of the nasogastric tube is avoided; the stomach is best kept empty by gravity drainage.
- A self-retaining catheter is introduced into the bladder to allow an accurate intake-output chart to be maintained.
- A central venous line is introduced for administration of IV fluids, and for monitoring central venous pressure (CVP). The earlier this line is inserted, the safer it is. Even in comatose bleeding patients, a central line is mandatory, despite the risk of bleeding that the procedure may entail.

Monitoring of the Patient

Clinical monitoring should include a chart of the grade of disturbed consciousness, the presence and degree of flapping tremors, the presence of fetor hepaticus, the liver size as obtained by palpation, as also by percussion of liver dullness in the thorax, the presence of free fluid within the abdomen, the degree of icterus, and the physical examination of the various organ systems of the body. Special emphasis should be laid on close monitoring of the respiratory rate, heart rate and rhythm, blood pressure, CVP, ECG, temperature and the intake-output chart.

Hepatic Encephalopathy

Sedation is avoided as far as possible; even the mildest sedation can appreciably increase the depth of coma. The patient however should be nursed in very quiet surroundings. Protein feeds are totally stopped. Metronidazole 400 mg 8 hourly is given orally through the nasogastric tube; amoxycillin 500 mg qds may also be given. Neomycin is best avoided because of possible nephrotoxic and ototoxic effects. It should be noted that metronidazole can be neurotoxic in hepatic failure. Rifaximin (800–1200 mg/day) is also effective against ammonia producing gut flora. It is however expensive and has not been recommended for routine use.

Lactulose 10–30 mL 8 hourly is administered orally, and the dose so adjusted as to allow 2–4 semisolid stools/day. Lactulose reaches the cecum unchanged, where it is broken down by bacteria to fatty acids. The drop in fecal pH promotes the growth of lactose fermenting organisms, but suppresses the growth of ammonia-forming bacteria. Lactulose may also detoxify short-chain fatty acids produced in the presence of blood and proteins within the gut. It significantly increases the colonic output of bacterial mass and soluble nitrogen; the latter thus becomes unavailable for absorption as ammonia.

Lactulose may cause significant diarrhea leading to hypernatremia and to volume depletion. The latter is to be avoided at all costs, as it compromises circulation and adversely affects renal function. Lactulose by enema (300 g in 500 mL normal saline) every 6 hours is given in patients with AHF who cannot tolerate oral or nasogastric administration.

A large bowel (colonic) wash or enema is given daily to evacuate the large bowel of nitrogenous products. In patients who have a GI bleed, lost blood should be promptly replaced. Lactulose and/or a mild purgative helps to hurry intestinal contents, and a bowel wash removes nitrogenous products released from the blood within the colon.

Furosemide should be avoided, and fluid and electrolyte balance should be well maintained; if disturbed, it should be quickly restored to normal. Endogenous benzodiazepine-like substances have been recovered from the cerebrospinal fluid (CSF) in patients with AHF. Flumazenil is a benzodiazepine receptor antagonist that has been used in a dose of 15–20 mg to provide temporary relief in patients with HE.

Exchange transfusion, charcoal hemoperfusion, plasmapheresis have all been tried to reduce serum ammonia levels but none of these procedures have been shown to increase survival.

Cerebral Edema

Cerebral edema combined with intracranial hypertension form the commonest cause of death in AHF when the intracranial pressure (ICP) is above 30 mm Hg. The optimal management of cerebral edema necessitates the maintenance of a balance between the mean arterial pressure and the ICP to preserve adequate cerebral perfusion. ICP monitoring may help in diagnosis and management of intracranial hypertension, especially in Grade 3 and Grade 4 encephalopathy. We have never used ICP monitoring; its use has not been shown to decrease mortality.[28] If monitored the ICP should be kept below 20 mm Hg and the cerebral perfusion pressure over 50 mm Hg. It is important to note that an arterial ammonia level over 200 ug/dL predicts brain herniation.[29]

Box 7: Preventive and therapeutic interventions for patients with cerebral edema and intracranial hypertension

- General measures—
  - Head of bed elevation to 30° angle, and maintain patient's neck in neutral position
  - Endotracheal intubation for grade III or IV hepatic encephalopathy
  - Minimize tactile and tracheal stimulation, including airway suctioning
  - Avoid hypovolemia and hypervolemia
  - Avoid hypertension
  - Avoid hypercapnia and hypoxemia
  - Monitor and maintain ICP <15 mm Hg
  - Maintain CPP >50 mm Hg
  - Monitor and maintain $SvjO_2$ between 55% and 85%
  - Use serial transcranial Doppler monitoring to titrate therapy
- Management of intracranial hypertension—
  - Mannitol boluses, 0.5–1.0 g/kg body weight or the use of hypertonic saline
  - Hyperventilation titrated to a $PaCO_2$ of 28–30 mm Hg
  - Induce moderate hypothermia to 32–33°C
  - Achieve serum sodium levels of 145–155 mEq/L
  - Induce coma with propofol or pentobarbital titrated to burst suppression of 5–10 cycles/sec
  - CVVH for oliguria and hyperosmolarity (>310 mOsm/L)

Abbreviations: CPP, cerebral perfusion pressure; CVVH, continuous veno-venous hemofiltration; ICP, intracranial pressure; $SvjO_2$, jugular bulb oxygen saturation.

Monitoring jugular bulb oxygen saturation through a jugular bulb venous catheter is also of help. A jugular bulb venous oxygen saturation less than 55% denotes cerebral ischemia; a saturation more than 85% generally denotes cerebral hyperemia. Intervention to prevent or counter intracranial hypertension can be made with the help of the above measurements.

Current recommendations to counter or prevent cerebral edema are briefly given below (Box 7)—

- Maintain the bed at a 30º angle with the patient's head in the midline.
- Episodes of increased intracranial hypertension should be countered by an IV bolus of 0.5–1 mL/kg mannitol. Between 100–150 mL of mannitol may be repeated twice in the day, though it is best not to exceed 400 mL. Decerebrate posturing, disturbances in ocular gaze, deepening of the unconscious state, systolic hypertension occurring singly or in combination are manifestations of increased intracranial hypertension. Corticosteroids have not been shown to be useful in reducing cerebral edema in patients with AHF.

- Coughing, prolonged suction through the endotracheal tube or tracheostomy should be avoided as these are associated with a rise in ICP.
- Hyperventilation so as to keep the partial pressure of carbon dioxide in the blood ($PaCO_2$) at 28–30 mm Hg can reduce ICP but the effect of this wears off in 24–48 hours.
- Excessive cerebral vasoconstriction can reduce perfusion. This can be detected by serial transcranial Doppler studies. Induction of mild hypothermia (core temp 32–33°C) induced by surface cooling or by the use of a special endovascular catheter has been shown to reduce ICP and cerebral blood flow and improve cerebral perfusion pressure in AHF.[30] Care must be taken to avoid shivering during induced hypothermia.
- There are reports that parenteral sodium pentothal or IV propofol can further reduce both cerebral blood and cerebral metabolic rate in refractory patients. We have never attempted this procedure as we are unconvinced whether the benefits outweigh the risk involved and also whether this intervention improves the final outcome.
- Hypertonic saline has been tried to induce hypernatremia with a view to countering cerebral edema (serum Na 145–155 mEq/L). There are many critical care units in the West that today prefer hypertonic saline to mannitol for reducing an increased ICP. If used, serum Na should be carefully monitored to prevent an acute rise in the serum Na. Indomethacin IV bolus has been reported in a few instances to reduce cerebral blood flow; this is by and large an unproven therapy and may perhaps do more harm than good.

Coagulopathy

Bleeding should be countered by titrated infusions of fresh frozen plasma (FFP) and by the infusion of packed red blood cells (RBCs). Administration of FFP does not improve survival; repeated infusions can cause volume overload with the added risk of transfusion induced lung injury. Massive bleeds are perhaps best countered by the infusion of recombinant factor VII. A worsening of coagulation parameters always denotes worsening liver function. Prevention of bleeding to a degree is possible by—

- Avoiding local trauma, including avoidable needle punctures.
- Avoiding a tracheostomy.
- Draining stomach contents by gravity rather than by suction.
- Avoiding corticosteroids.
- Using oral sucralfate, proton pump inhibitors or H_2 receptor antagonists intravenously prophylactically in the prevention and treatment of GI bleeding.

Renal Failure

The presence of renal failure in patients with AHF denotes a grave prognosis. Renal failure due to acute tubular necrosis occurs in close to 70% of patients with AHF. The mechanisms responsible for renal failure include—

- Renal hypoperfusion due to hypovolemia, hypotension.
- Evolution of a systemic inflammatory response syndrome.
- Evolution of the hepatorenal syndrome.
- Toxic effects of the etiological agents e.g. acetoaminophen, phosphorus, poisonous mushrooms and toxic effects of nephrotoxic drugs or radiographic contract agents.

Careful monitoring of urine output vis-à-vis fluid intake, serum creatinine, urinary Na concentration is important. Diuretics or renal dose of dopamine are of no use in prevention or treatment of renal failure. Continuous venovenous hemofiltration (CVVH) may be necessary to preserve fluid electrolyte balance. CVVH is preferred to hemodialysis as it avoids rapid fluid shifts and sudden changes in ICP that tend to occur with intermittent hemodialysis.

Maintenance of Fluid and Electrolyte Balance

Fluid and electrolyte balance should be assiduously maintained. Serum sodium levels tend to be low in acute hepatic failure. Severe persistent hyponatremia is a pointer to impending cell death. Hyponatremia due to obvious salt loss from the body (as with the use of diuretics) is corrected by the use of normal saline; hypertonic saline should be avoided as far as possible.

Hypokalemia and metabolic alkalosis are frequently observed. The latter potentiates ammonia toxicity. Hypokalemia is due to nasogastric suction, loss of K^+ from the urine and stools, to the use of IV dextrose-insulin, and to a poor intake of potassium. In the presence of a good urine output, 80–120 mEq of potassium may need to be given in an infusion daily. In the terminal stages, or in the presence of renal failure, hyperkalemia is observed.

Serum calcium levels may be low; 10 mL of 10% calcium gluconate may need to be given intravenously once or twice daily.

Total fluid intake should balance urine output and the loss of other secretions. The CVP should be maintained around 7–8 cm H_2O, and should as far as possible not exceed 12 cm H_2O. Salt-free albumin is often given intravenously to counter hypoalbuminemia, and to maintain an effective circulating volume.

Nutrition

All dietary protein should be stopped till recovery ensues. A few days to a few weeks of protein deprivation is well tolerated by these patients. 1500–2000 calories are supplied daily as 20% dextrose through a gastric drip. Strained vegetable soup, also given through the nasogastric tube, provides the necessary minerals and some additional carbohydrates. 20% dextrose is given intravenously through a central line; potassium may be added to the dextrose drip. If blood sugar levels are high, an appropriate dose of insulin may be added to the dextrose infusion. Vitamins B, C and K, together with a multivitamin preparation are also given intravenously daily.

Vegetable proteins are started only when recovery is evident. Ten grams are given orally to start with; this is gradually increased as recovery progresses.

In massive hepatic necrosis, there is an increase in the plasma levels of the aromatic amino acids methionine, tyrosine, and phenylalanine, and a decrease in the branched chain amino acids leucine, isoleucine and valine. Infusion of branched chain amino acids has been recommended in the management of hepatic coma, but is not of proven value. Branched chain aminoacids contained in specially made formulations, can also be used orally.

Hypoglycemia

Persistent intractable hypoglycemia is of ominous significance,[31] and can cause sudden death in these patients. It is countered by a continuous infusion of 20% dextrose. 100 mL of 50% dextrose may need to be given in addition, and should be repeated when blood glucose levels are below 70 mg/dL.

Acid-Base Disturbances

Lactic acid acidosis is frequent in patients who are deeply comatose. It may occur even with a normal arterial blood pressure, and is perhaps due to arteriovenous shunting, to capillary endothelial damage, and to poor uptake and utilization of oxygen by tissue cells. This is also of ominous significance, and is countered by improving oxygen delivery or transport to the optimal level. The use of sodium bicarbonate grants only a temporary reprieve.

In the early phases of acute hepatic failure, respiratory alkalosis is common. In the presence of hypokalemia, a mixture of respiratory and metabolic alkalosis may produce a significant increase in the pH. Potassium should be replaced by a slow IV infusion. Metabolic acidosis ultimately occurs either due to lactic acid acidosis, or to uremic acidosis, or to both factors. Mixed acid-base disorders may be frequently observed.

Respiratory Failure

Respiratory failure requires expert management. Lung function is impaired for various reasons. Infection, aspiration of gastric contents, atelectasis, and non-cardiogenic pulmonary edema, all play a part and contribute to a low PaO_2. Patchy shadows develop within the lung and continue to increase. Acute lung injury (ARDS) is the most dreaded of all complications, as it is always fatal when it occurs secondary to fulminant hepatic disease.

It is vital to secure the airway by endotracheal intubation, as soon as the gag reflex is impaired and the patient is slightly obtunded. We prefer the early use of mechanical ventilation to ensure full oxygen saturation of arterial blood. ARDS is a dreaded complication and requires skillful handling (see Chapter Acute Lung Injury and Acute Respiratory Distress Syndrome). *It is worth noting that, in a patient with acute hepatitis, an unexplained increase in the respiratory rate may be an early sign of impending acute hepatic failure.*

Circulatory Failure

Volume depletion should be guarded against and promptly corrected. Large quantities of volume infusion to maintain blood pressure, often precipitate acute lung injury (ARDS). If filling pressures are adequate and arterial blood pressure is still below 100 mm Hg, inotropic support with dopamine and/or vasopressor support with norepinephrine should be commenced.

Arrhythmias are frequent in the terminal phase. Hypokalemia and hyperkalemia are easily correctible causes of dangerous arrhythmias.

Infection

Infections are common and may be easily missed unless the intensivist has a high index of suspicion. Fever and leukocytosis may be absent. Worsening encephalopathy, hypotension, hemodynamic instability, a fall in oxygen saturation or just overall worsening of the clinical condition should promptly arouse suspicion, particularly when liver function has started to recover prior to the setback.

Urinary infection, respiratory infection and sepsis iatrogenically introduced through central lines and catheters, are frequent in spite of the best intensive care offered to these patients. Patients with acute hepatic failure are immunocompromised to some extent, and acute Gram-negative bacterial sepsis is often observed. Appropriate antibiotics are invariably necessary. Aminoglycosides should not be used as far as possible in the presence of renal dysfunction. Blood cultures, cultures of catheter tips, bacteriological examination of urine and sputum, are always performed. Fungal infections may be overlooked as blood cultures are not always positive. They should be suspected when the patient deteriorates after an initial improvement, and in the presence of leukocytosis, renal dysfunction and pyrexia not responding to antibiotics. Antifungal agents should be used with care because of potential hepatic and renal toxicity. Scrupulous attention to aseptic suction through the endotracheal tube, and to careful handling and protection of central venous lines must be given to prevent iatrogenic infection.

Acute Pancreatitis

This is a dreaded complication of fulminant hepatitis. It should be suspected in the presence of—

- Severe upper abdominal pain.
- A sudden deterioration in the clinical state.
- A marked tenderness in the abdomen.
- Rapid development of free fluid within the abdomen.

A marked rise in serum amylase is observed in most, but not all patients. Pancreatitis in AHF can be due to the hepatitis virus, to shock, sepsis, corticosteroid therapy, or bleeding within the pancreas. It carries virtually a hopeless prognosis.

It should be noted that corticosteroids are not found to be of any use in AHF; in fact they may well produce further complications—gastric erosions, infection, pancreatitis.

Therapy Directed to the Specific Etiology Causing AHF

If the etiology of AHF in a patient has been determined, specific therapy can be offered (depending on the etiology) so as to lessen or reverse the liver injury. If specific therapy is available it should be given promptly.

Acetaminophen Poisoning or Overdose

N-acetyl cysteine (NAC) is a specific antidote for acetaminophen poisoning. The drug is given intravenously within 8–10 hours after an acute overdose. It prevents hepatotoxicity through the replenishment of glutathione. NAC may however remain effective, but to a much lesser extent up to 72 hours after acetaminophen ingestion.

Non-acetaminophen Induced AHF

NAC has been found to be useful also in non-acetaminophen induced AHF and should therefore be administered is all patients with AHF. The drug has been shown to result in increased survival, and to reduce brain edema; it has been shown to benefit oxygen delivery, oxygen consumption and the overall hemodynamic profile.

A randomized controlled trial of NAC by the US Liver Failure Study Group in patients with non-acetaminophen induced AHF showed improved transplant free survival.[32] In a randomized controlled trial NAC appeared to improve spontaneous survival when given during stages I and II of encephalopathy in patients with non-acetaminophen liver cell failure. These patients included those with drug-induced liver injury and hepatitis B infection.

Mushroom Poisoning

Patients with acute liver failure secondary to mushroom poisoning should be promptly given penicillin G intravenously in a dose of 500,000–1 million units/kg per day. Silibinin is even more efficacious than penicillin. Though available in Europe and South America, it is not available in the United States or in India.

Viral Hepatitis

Nucleotide analogues should be considered for hepatitis B associated liver cell failure (if a significant viral load is detected in the blood) and for prevention of post-transplant recurrence. Patients with proven or suspected herpes virus or Varicella zoster virus as the cause of AHF should be given acyclovir—10 mg/kg IV every 8 hours. Cytomegalovirus infection causing AHF should be treated with gancyclovir with appropriate dosing.

Wilson's Disease

This is an uncommon cause of AHF. Early diagnosis is critical, otherwise the disease is always fatal. A high bilirubin (mg/dL) to alkanine phosphatase (IU/L) ratio should arise suspicion of this disease. Copper lowering measures including the use of penicillamine should be tried. Plasmapheresis, hemofiltration and albumin dialysis serve merely as temporary measures before liver transplantation. These patients invariably need liver transplantation.

Autoimmune Hepatitis

The presence of autoimmune antibodies confirm the etiology. But autoimmune antibodies may be absent in close to 30% of cases. Liver biopsy through the transjugular route is recommended to confirm or disprove the diagnosis when autoimmune hepatitis is suspected in the absence of autoimmune antibodies.

Corticosteroid therapy is instituted—either methyl prednisolone 20–40 mg IV 8 hourly or 60 mg prednisolone/day orally. Patients should be considered for a transplant even when corticosteroids are being administered.

Acute Fatty Liver of Pregnancy

For acute fatty liver of pregnancy causing the HELLP (hemolysis-elevated liver enzymes-low platelets counts) syndrome prompt delivery of the fetus generally leads to recovery. If hepatic failure persists after delivery, the patient is recommended liver transplantation.

Acute Ischemic Injury

Treatment is directed toward cardiovascular support and to the management of shock causing severe ischemic injury to the liver.

Mortality

For patients with AHF due to acetaminophen overdose, hepatitis A virus infection, shock or pregnancy related acute liver failure, the short-term survival without transplantation is over 50%. The short-term transplant free survival in AHF due to drugs, HBV infection, autoimmune hepatitis, Wilson's disease, Budd-Chiari syndrome and due to indeterminate causes is less than 25%. Bad prognostic features which should prompt consideration for a hepatic transplant have been listed in the King's College Criteria System (see below). These criteria have however been criticized on the basis of low sensitivity and negative predictive values, especially in patients with AHF due to causes other than acetaminophen toxicity.

A brief mention must be made of other scoring systems. The Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system is found to be as good as the King's College criteria in predicting death in acetaminophen induced AHF.[33]

The Cliché scoring system[33] involves estimation of various clotting factors. This requires high technical expertise and is not suited to developing countries. Other prognostic markers include the degree of hepatic necrosis as judged by a liver biopsy performed through the transjugular route, the amount of fresh frozen plasma required to correct coagulopathy and the determination of sensory evoked potentials.

PROGNOSIS AND CRITERIA FOR LIVER TRANSPLANTATION

AHF associated with Grade 4 encephalopathy has over 80% mortality without an orthotropic liver transplant. Prognosis depends on age, etiology, severity of liver cell necrosis, the degree of coagulopathy and encephalopathy, and the duration of the illness. Serum phosphate levels more than 1.2 mmoL/L on days 2 and 3, and blood lactate levels more than 3 mmoL/L are believed to be associated with a poor prognosis. Finally, Model for End-stage Liver Disease (MELD) score more than 32 denotes poor survival.

The fact remains that the main definitive treatment for AHF is a liver transplant. The successful use of orthotropic liver transplant has made it imperative to determine prognostic indicators to select patients who are most likely to benefit from orthotropic liver transplantation. Donor liver transplants play an important role in a few liver transplant centers. In India liver transplantation is being performed in different centers, those with the maximum experience and with results comparable to good centers in the West being in Delhi and Chennai. Mumbai unfortunately lags behind in this field. The paucity of cadaver donors (though this has improved substantially) and the poor infrastructure which hinders the prompt use of donor organs for transplant purposes in patients with AHF are some of the hurdles that afflict transplant liver surgery in India.

There are many prognostic systems that lay down criteria for liver transplantation in patients with AHF. The most frequently used scoring system consist of criteria laid down by King's College (King's College criteria).[34] These are tabled in Box 8.

In transplant centers, the chief contraindications to hepatic transplant include a cerebral perfusion pressure less than 50 mm Hg for more than 2 hours despite therapy, ongoing sepsis, fraction of inspired oxygen (FiO_2) requirement more than 60%, uncal herniation with dilated pupils, and brain damage caused by an intracranial bleed. Patients desperately needing a transplant may need to wait for lack of a donor organ, and may die before this is available. The current strategies in good transplant centers that help to tide over this possible waiting period are the use of artificial or bioartificial livers, hepatocyte transplantation and extracorporeal perfusion.

Box 8: King's College criteria for liver transplant

Acetaminophen overdose—
- Arterial pH <7.3 (irrespective of grade of encephalopathy or
- PT >100 sec (INR >6.5)
- Serum creatinine >3.4 mg/dL (>300 µmoL/L)
- Patients with Grades III and IV hepatic encephalopathy

Non-acetaminophen liver injury—

PT >100 sec (INR >6.5) (irrespective of grade of encephalopathy) or any three of the following variables—
- Age <10 or >40 years
- Non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
- Jaundice >7 days before onset of encephalopathy
- Serum bilirubin ≥17.4 mg/dL (300 UmoL/L)
- PT >50 seconds

Abbreviations: INR, international normalized ratio; PT, prothrombin time.

CRITICAL CARE OF COMPLICATIONS IN CHRONIC LIVER CELL FAILURE

Patients with chronic liver cell dysfunction need intensive care when they develop an acute hepatic encephalopathy (i.e. acute on chronic liver failure), a severe GI bleed, an acute infection, or develop oliguric renal failure. More than one of these complications often coexist in the same patient.

Acute Hepatic Encephalopathy

Acute hepatic encephalopathy in a cirrhotic patient may occur spontaneously in the natural course of events, usually as a terminal feature in a patient who has ascites and is deeply jaundiced. More often than not, acute encephalopathy in cirrhotics is precipitated by factors which further depress liver cell function, and increase nitrogenous material within the gut. These precipitating factors should be sought for, recognized and rectified as a matter of immediate priority after admission to the ICU.

Precipitating factors—

- Use of furosemide or other diuretics, volume loss, and subtle electrolyte disturbances even in the absence of significant hypovolemia. These can trigger acute neuropsychiatric features.

  Paracentesis involving removal of a large quantity of ascitic fluid is an important precipitating cause of coma. Again electrolyte imbalance following removal of large quantities of electrolytes and water, hypotension and changes in the hepatic circulation may be contributory factors. These changes are not necessarily reflected by disturbances in serum electrolytes.
- Fluid and electrolyte loss from vomiting, diarrhea or from inadequate fluid intake.

  The above precipitating factors can be corrected by IV infusions of fluid and electrolytes, and restoring electrolyte balance. Correction of hyponatremia and hypokalemia are of prime importance. Hypovolemia can be quickly corrected by the IV infusion of salt free albumin. Hypotension, which persists after volume replacement should be treated by inotropic (dopamine) and/or vasopressor support.

  Therapeutic paracentesis for ascites should not be performed in patients who are severely ill with chronic

Box 9: Selection of patients for therapeutic paracentesis

- Tense ascites
- Preferably with edema
- Child's Grade B
- Serum bilirubin <10 mg/dL
- Platelets >40,000/mm^3
- Serum creatinine <3 mg/dL
- Urinary sodium >10 mEq/24 hour
- PT >50 seconds

Source: Sherlock S. Diseases of the Liver and Biliary System. London, Oxford: Blackwell Scientific Publications; 1989.

liver cell dysfunction, as this can precipitate both hepatic encephalopathy and acute oliguric renal failure.

The indications and precautions for therapeutic paracentesis[35] are tabled in Box 9.

- Gastrointestinal bleeds or blood loss from any other source is one of the most important precipitating factors. It may be occult and may not manifest immediately. A rectal examination may reveal the presence of melena and should always be performed as part of a routine examination. Coma in these patients may be due to hypovolemia, hypotension, presence and absorption of increased proteins and their breakdown products from blood within the gut, and also to anemia if there is a significant drop in the hemoglobin. Even a mild GI bleed in decompensated cirrhotics needs to be replaced by a blood transfusion. A laxative to evacuate the intestinal contents of blood, and a bowel wash, should also be promptly given.
- *Infection* This is an important precipitant; its source and nature should be sought for, identified and treated. Commonly, infection involves the lungs and urinary tract. Spontaneous bacterial peritonitis is characterized by the presence of infected ascitic fluid in the absence of a recognizable cause of secondary peritonitis.[36] It can result in a rapidly evolving acute encephalopathy in cirrhotics, and should always be suspected when a patient with cirrhosis deteriorates suddenly without any apparent cause. The clinical features include pyrexia, diffuse or localized abdominal pain on palpation. These features may however be absent, and the diagnosis is made only when a high index of suspicion results in the examination of ascitic fluid which shows more than 250 polymorphs/mm^3. The association of a pH less than 7.3 and polymorphs more than 500/mm^3 in the ascitic fluid, is diagnostic of bacterial peritonitis.[37] The infection is generally blood borne and usually monomicrobial. Patients with cirrhosis are immunocompromised and prone to bacteremia. Ascitic fluid is a good culture medium for bacterial growth. If the opsonic activity of ascitic fluid is very low, there is poor opsonic coating of bacteria within the fluid; bacteria are therefore not destroyed by polymorphs, and produce a peritonitis. Culture of ascitic fluid in our limited experience, is rarely positive. At times infection of the peritoneum is not blood borne, but occurs through the gut wall, pointing to poor immune defenses that allow a breach of the gut wall by intestinal flora. Infecting organisms are Gram-negative *E. coli* or *Streptococci.*

  Broad-spectrum antibiotics (third generation cephalosporin, cefotaxime) should be used under the following conditions—
  - When clinical features are typical of spontaneous bacterial peritonitis.
  - When the ascitic fluid shows polymorphs more than 250/mm^3 and the clinical picture is compatible with a bacterial peritonitis.
  - When the ascitic fluid shows a polymorph count more than 500/mm^3 even in the absence of symptoms or signs of peritonitis. Therapeutic paracentesis should be done.

  Prognosis is grave; it depends on the severity of bacterial infection of the peritoneum, the degree of underlying liver cell dysfunction, and the degree of clinical deterioration precipitated by the infection. The survival rate over a year in those patients who are discharged from the hospital, is dismal, being less than 2–38%.
- *Stress* in the form of surgery, trauma, fracture, shock or anesthesia can further depress hepatic function.
- *Acute alcoholic bouts* Ingestion of alcohol precipitates drowsiness and coma both by producing an associated acute alcoholic hepatitis, and by depressing cerebral function. Sudden alcohol withdrawal can also precipitates neuropsychiatric disturbances which may be difficult to distinguish from hepatic encephalopathy.
- *Sedatives*, even if mild or in small doses, are an important cause of neuropsychiatric symptoms and acute encephalopathy. They should be strictly avoided in all cirrhotics.
- *Constipation*, sometimes triggers encephalopathy probably by increasing the nitrogenous content within the bowel and providing for a larger source of ammonia products.
- *A large protein meal* acts in a similar fashion, and its effect is accentuated by the presence of constipation.

Hepatic encephalopathy is treated on the lines already elaborated upon in acute hepatic failure. It is obvious that the prognosis is better if a precipitating factor is identified and quickly corrected.

In the absence of a past history it is often difficult to determine whether acute encephalopathy, jaundice and deranged liver cell functions are due to acute hepatocellular dysfunction in a patient with a previously normal liver, or are due to acute on chronic liver cell failure. A poor nutritional state, a firm enlarged spleen, a firm and at times irregular liver with presence of spider nevi, point to acute on chronic liver cell dysfunction.

Neuropsychiatric features in acute on chronic liver cell failure are commonly misdiagnosed as acute alcoholic

intoxication or alcohol withdrawal syndrome. A wrong diagnosis of a manic or depressive psychosis may also be made. Symptoms are at times bizarre, and may be transient lasting for only 8–12 hours. We have seen such abnormal neuropsychiatric behavior necessitating admission, after ingestion of a large meal or following constipation, in patients with cirrhosis. A good clinical examination for gynecomastia, liver palms, spider nevi, and for other clinical and biochemical evidence of liver cell dysfunction will always clarify the diagnosis.

Severe Gastrointestinal Bleeding

Acute GI bleeding in a cirrhotic patient is a dreaded emergency requiring critical care. GI bleeds are most commonly due to bleeding esophageal or gastric varices. They could also result from acute gastroduodenal erosions, a Mallory-Weiss syndrome, or a chronic peptic ulcer. The present discussion is related to the diagnosis and management of variceal bleeding in cirrhotics in an ICU setting (Flowchart 1).

Diagnosis of Variceal Bleeding

The diagnosis is made because of hematemesis or melena or both in a cirrhotic patient. If the patient is in hospital, fresh or altered blood may be present on aspiration of the nasogastric tube if this is already in place. The bleeding however may not be always evident. A slow ooze may fill the gut with blood before the bleed is recognized. A rectal examination may demonstrate melena and may allow an earlier diagnosis to be made in a cirrhotic who shows clinical deterioration.

The possibility of an upper GI bleed (generally variceal in origin) should always be suspected if a cirrhotic develops a sudden encephalopathy, becomes hypotensive and shows features of hypovolemia or has a sharp fall in urine output.

Variceal hemorrhage constitutes the second most overall common cause of upper GI bleeds. Varices in the upper GI tract are present in almost all patients with advanced cirrhosis of liver with portal hypertension. The varices that bleed are generally present in the lower esophagus and stomach. The propensity for variceal bleeding is chiefly determined by the pressure gradient in the hepatic veins.

Mortality of variceal bleeding in spite of improvement in medical management is 20% in the first 6 weeks.[38] The rebleeding rates are as high as 30–40% in the first 6 weeks and is associated with a 30% mortality.[39]

As soon as variceal bleeding is suspected (and this is the most likely cause in a cirrhotic) terlipressin or somatostatin or the somatostatin analog octreotide should be administered. If possible, pharmacological therapy should be administered during transport or immediately on admission to the hospital. These drugs can arrest or control hemorrhage in varices in more than 60% of patients and can also help endoscopic visualization by reducing active bleeding. Terlipressin is the only drug shown to reduce mortality.[40,41] It is administered IV in a dose of 2 mg every 4–8 hours followed by half this dose for 5–7 days. Somatostatin is also useful and acts through splanchnic arteriolar constriction, thereby reducing the inflow of blood into the portal venous circulation. The dose is 250 mg IV as a bolus, repeated every 3 hours followed by an infusion of 250 ug/hour for 5–7 days to prevent rebleeding.[42]

Octreotide has a longer half-life compared to somatostatin and is administered as a 50–100 mg IV bolus followed by a continuous infusion of 25–50 μg/hour. Both somatostatin and octreotide have the same effect in controlling variceal bleeding, yet when used alone they do not decrease mortality.[43,44] The use of these drugs should always be promptly followed by endoscopy.

In many units in peripheral hospitals outside main cities neither terlipressin, somatostatin nor octreotide are available. When unavailable vasopressin can be given to control variceal bleeding. It is administered in an IV infusion starting at 0.4 U/minute, the infusion rate being increased to 1 U/minute depending on the clinical response. Side effects of vasopressin include myocardial ischemia, cerebrovascular accidents, limb ischemia and hyponatremia. These are dangerous complications and occur in a significant number of patients. Therefore, it is important to concurrently administer IV nitroglycerin in a titrated dose (10–30 μg/minute). Vasopressin reduces or arrests variceal bleeding in 80% of patients but it does not decrease mortality, perhaps because of vascular constriction with resulting ischemia to other organ systems.

Antibiotics should be administered if there is any suspicion of infection. Many units prefer to use prophylactic antibiotics as they have been shown to reduce the incidence of infection as also reduce early rebleeding and improve survival in these patients. Ceftriaxone is the drug most commonly used. Fluoroquinolones form an alternative particularly in patients with a history of penicillin allergy.

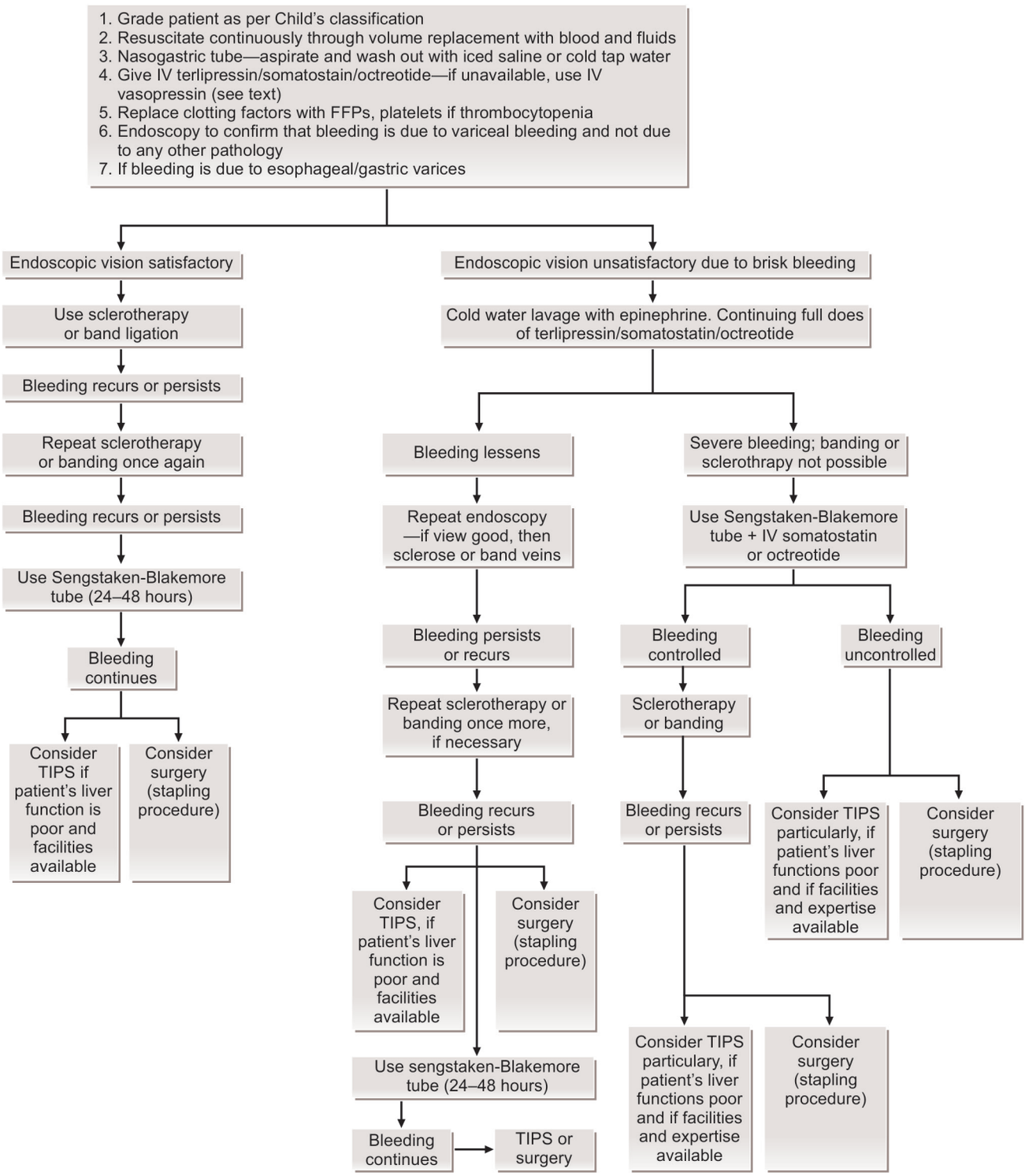
Endotracheal intubation may be necessary to secure the airway in obtunded patients, if there is a risk of aspiration and in the presence of impending hepatic encephalopathy.

While the above mentioned pharmacological therapy is in progress, the patient should simultaneously receive resuscitation with crystalloids and packed RBCs to quickly correct hypovolemia and restore a normovolemic state. Uncorrected hypovolemia or delay in correcting hypovolemia can cause complications, in particular renal failure. Yet, overcorrection so as to cause a hypervolemic state should be avoided as this could perpetuate or even exacerbate variceal bleeding.

Many of these cirrhotic patients are deficient in clotting factors and have an INR well above normal as also a raised APTT. Fresh frozen plasma should be administered to decrease the PT to acceptable levels (if possible, INR of 1.4–1.6). Advanced cirrhosis is associated with low fibrinogen levels for which several units of cryoprecipitate need to be given. Uncorrected clotting abnormalities will allow variceal bleeding to continue.

Following resuscitation, and the pharmacologic therapy indicated above, endoscopy should be performed to determine the exact source of bleeding. Though esophageal

Flowchart 1: Management of variceal bleeding


1. Grade patient as per Child's classification
2. Resuscitate continuously through volume replacement with blood and fluids
3. Nasogastric tube—aspirate and wash out with iced saline or cold tap water
4. Give IV terlipressin/somatostain/octreotide—if unavailable, use IV vasopressin (see text)
5. Replace clotting factors with FFPs, platelets if thrombocytopenia
6. Endoscopy to confirm that bleeding is due to variceal bleeding and not due to any other pathology
7. If bleeding is due to esophageal/gastric varices
Endoscopic vision satisfactory
Use sclerotherapy or band ligation
Bleeding recurs or persists
Repeat sclerotherapy or banding once again
Bleeding recurs or persists
Use Sengstaken-Blakemore tube (24–48 hours)
Bleeding continues
Consider TIPS if patient's liver function is poor and facilities available
Consider surgery (stapling procedure)
Endoscopic vision unsatisfactory due to brisk bleeding
Cold water lavage with epinephrine. Continuing full does of terlipressin/somatostatin/octreotide
Bleeding lessens
Repeat endoscopy —if view good, then sclerose or band veins
Bleeding persists or recurs
Repeat sclerotherapy or banding once more, if necessary
Bleeding recurs or persists
Consider TIPS, if patient's liver function is poor and facilities available
Consider surgery (stapling procedure)
Use sengstaken-Blakemore tube (24–48 hours)
Bleeding continues
TIPS or surgery
Severe bleeding; banding or sclerothrapy not possible
Use Sengstaken-Blakemore tube + IV somatostatin or octreotide
Bleeding controlled
Sclerotherapy or banding
Bleeding recurs or persists
Consider TIPS particulary, if patient's liver functions poor and if facilities and expertise available
Consider surgery (stapling procedure)
Bleeding uncontrolled
Consider TIPS particularly, if patient's liver functions poor and if facilities and expertise available
Consider surgery (stapling procedure)

and gastric varices are undoubtedly the commonest source of bleeding in cirrhotic patients, in close to 20–25% of patients GI bleeding may occur from a non-variceal source.

Endoscopic treatment of esophageal varices consists of sclerotherapy or band ligation, depending on the experience and expertise of the endoscopist. Band ligation is today the treatment of choice as it reduces the risk of a recurrent bleed (compared to sclerotherapy) and has fewer complications. Banding may however at times be impossibly difficult in a patient with massive bleeding. In these patients sclerotherapy needs to be attempted. Complications following sclerotherapy include mucosal ulcers that have

opened in submucous venous channels. Rebleeding is seen in 30% of cases, either from remaining varices or ulcers. The former require sclerotherapy; omeprazole helps to arrest bleeding from ulcers. Esophageal strictures can result from chemical esophagitis and acid reflux. Rarely perforation of the esophagus or even an esophagobronchial fistula may result. Pulmonary complications include aspiration pneumonia, pleural effusion, mediastinitis. Pyrexia is frequent after sclerotherapy and bacteremia may occur during or following the procedure necessitating the use of appropriate antibiotics.

Band ligation (the varices being identified, ligated and strangulated by the application of O-bands through the endoscope) is comparatively free of complications. Ulcers may occur at the site of previous bands and torrential hemorrhage can occur if the band slips.

The success of endoscopic treatment is 80–85%, roughly similar to the use of vasoactive drugs.[45-48] However, despite similar success rates, a recent Cochrane meta-analysis concluded that band therapy or sclerotherapy could not be recommended as a first-line therapy and that it should be used only when pharmacological treatment has failed. In practice, pharmacological therapy is followed by endoscopic treatment.

Gastric varices generally bleed less than esophageal varices and are treated with sclerotherapy with *histoacryl* glue. Complications include ulceration of the mucosa and embolic events from the glue.[49]

If in spite of the above procedures bleeding persists or is too profuse to allow emergency endoscopic banding or sclerotherapy, an attempt is made to arrest the bleeding by the insertion of the Sengstaken-Blakemore tube. This is a four-lumened tube that has an esophageal and gastric balloon,[50] a tube in the stomach and a fourth lumen for continuous aspiration of the esophagus above the esophageal balloon. The lubricated tube is passed orally into the stomach which is emptied, and the gastric balloon is inflated with 250 mL air and is doubly clamped. The gastric tube is aspirated continuously. The esophageal balloon is inflated to a pressure of 40 mm Hg slightly more than the expected portal vein pressure. Firm traction is exerted on the tube with the help of a suitable device, for 24 hours. Traction is then released and the esophageal balloon deflated; the gastric balloon is kept inflated for a further 24 hours. If bleeding recurs, the esophageal balloon may be reinflated and traction reapplied for a further 24–48 hours, or till emergency band ligation, sclerotherapy or surgery can be done.

In experienced hands, the Sengstaken-Blakemore tube often temporarily stops variceal bleeding and allows emergency banding or sclerotherapy. It is the only immediate expedient available for stopping profuse life-threatening blood loss. Unfortunately it requires great expertise for correct use, and complications are frequent. These include asphyxia due to migration of the esophageal balloon upward into the pharynx, ulceration of the esophagus and aspiration pneumonia.

However, if bleeding persists in spite of the Sengstaken-Blakemore tube and band ligation or sclerotherapy is not possible, or if the bleeding continues following band ligation or sclerotherapy, transjugular intrahepatic portosystemic shunt (TIPS) or emergency surgery is warranted.

TIPS[51]

The transjugular intrahepatic portosystemic shunt (TIPS) is a comparatively new non-operative therapeutic option for the management of severe variceal bleeding particularly in patients with poor liver function (Grade C of Child's classification), awaiting a liver transplant. TIPS once securely placed reduces the hepatic vein pressure gradient and stops bleeding in 90–100% of cases. The emergency placement of TIPS is however associated with a high mortality (50%), and a high incidence of hepatic encephalopathy. It is important to attempt TIPS to arrest variceal bleeding only if full medical treatment (use of vasoactive drugs, sclerotherapy or banding) has failed. The procedure is performed under sedation and local anesthesia using ultrasound control. The middle hepatic vein is catheterized through the transjugular route and a needle is inserted through the catheter (under ultrasound guidance) and through the liver parenchyma, into a main portal vein branch. A guide wire is introduced through the needle and the catheter advanced into the portal vein. The needle is removed and the portal vein gradient measured. The needle tract is dilated by a balloon, and a self-expanding metal stent is inserted and expanded to 8–12 mm. A portosystemic shunt is thus established; reduction in portal vein pressure should arrest variceal bleeding. TIPS seems more effective in controlling and preventing variceal bleeding than band ligation or sclerotherapy.

Complications chiefly include hemorrhage (intra-abdominal, biliary, or through the liver capsule), infection, and stent stenosis or occlusion. Early occlusion is seen in 12% and is usually due to thrombosis within the shunt. Shunt occlusion results in recurrence of variceal bleeding. Late occlusion is due to intimal proliferation at the hepatic venous end of the stent. Other complications are—TIPS encephalopathy (due to portosystemic shunt), renal failure (due to excessive intravenous contrast used). Hepatic infarction can occur from misplacement of the stent into the right hepatic artery.

Emergency Surgery

Emergency surgery for bleeding esophageal varices has been considerably reduced following the use of vasoactive drugs, endoscopic banding or sclerotherapy, balloon tamponade and TIPS. When these fail or if the expertise for performing TIPS is unavailable in patients who rebleed after banding or sclerotherapy, emergency surgery is warranted. Esophageal transection using the stapling procedure is the surgery of choice. Stapling arrests hemorrhage, but death occurs in 30–40% of patients from hepatocellular failure. Alternative emergency surgical procedures are a mesocaval or portocaval shunt. Both are associated with a high mortality and a high incidence of hepatic encephalopathy in Grade C patients. In our setup we rarely advocate emergency surgery in patients categorized as under Grade C of Child's classification.

Prevention of Bleeding

Propranolol decreases the risk of recurrent variceal bleeding but has little effect on survival. It is of value in gastropathy. Isosorbide mononitrate also reduces the risk of variceal bleeding. Both propranalol and isosorbide mononitrate should be used as a preventive measure.

Various portal-systemic shunt procedures are used to prevent recurrent gastroesophageal variceal bleeding. These include portocaval, mesocaval or splenorenal shunts. For poor risk patients the mortality is 50%; in good risk patients it is about 5%. Hepatic encephalopathy is an important complication of portocaval shunts. Myelopathy with paraplegia and a Parkinsonian picture are other complications.

Hepatic transplant is the optimal solution to recurrent bleeding varices in cirrhotic patients. Previous sclerotherapy or portosystemic shunts do not affect post-transplant survival.

Complications of variceal bleeding include hypotensive shock, hepatic encephalopathy, supervening infection, aspiration pneumonia and renal failure. Prompt treatment of variceal bleeding reduces the incidence of these complications.

Acute Infections

Patients with chronic liver cell dysfunction need intensive care if there is a serious, often life-threatening infection. Bacteremia with sepsis is an important, life-threatening complication in these patients. The source of bacteremia is generally undetermined. The role of translocation of bacteria from the gut in patients with impaired liver cell function may have a significant role both in initiating and perpetuating sepsis. As mentioned earlier, acute infection involving any organ system, invariably worsens liver cell function and may well precipitate hepatic encephalopathy. In cirrhotics, body responses to infection may not be as vigorous as in patients who are normal to start with. Fever may be low grade, physical findings may be meagre, and leukocytosis may be absent. In the absence of a definite source of infection, the possibility of a specific bacterial peritonitis should always be excluded by examination of the ascitic fluid (see previous section of this chapter). Patient care demands the prompt use of empiric therapy with antibiotics after blood cultures and other relevant cultures and microbiological tests have been sent for examination. The antibiotics frequently used are a third generation cephalosporin or ciprofloxacin. If there is a possibility of a staphylococcal infection, vancomycin needs to be added (see Chapter The Immunocompromised Patient).

Acute Oliguric Renal Failure

Acute renal failure could be due to prerenal causes or to acute tubular necrosis. Prerenal causes include hypovolemia, blood loss, hypotension from any cause, or fluid and electrolyte disturbances. Paracentesis of a large volume of ascitic fluid or overvigorous diuretic therapy often precipitates oliguric renal failure. Acute tubular necrosis may occur in some of these patients. The hepatorenal syndrome as mentioned earlier, is characterized by progressive acute oliguric renal failure in the presence of normal tubular function.

Table 1: Iatrogenic causes of oliguric renal failure (and their treatment) in chronic liver cell failure

Causes	*Treatment*
• Drugs—	
– Diuretics or Lactulose	Volume expansion
– Non-steroidal antiinflammatory drugs	Stop drugs
– Aminoglycosides	Stop drug
– Cyclosporine	Hemodialysis
• Paracentesis of large volume of ascitic fluid	Volume expansion
• Volume depletion (blood loss or vomiting or diarrhea)	Volume replacement

Volume replacement, replacement of blood loss to improve the urine output, should be prompt. The prognosis of a fully evolved hepatorenal syndrome is well-nigh hopeless. Iatrogenic and other potentially correctible problems causing oliguric renal failure are listed in Table 1. They should be carefully assessed and as far as possible corrected. Even so, the prognosis in the presence of azotemia is grim.

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CHAPTER 55

Acute Pancreatitis

INTRODUCTION

Acute inflammation of the pancreas can be of varying severity. Mild or acute edematous pancreatitis has a good prognosis and recovery almost always ensues. These patients can be managed in the general wards of a hospital. However, in about 30% of patients the inflammation is severe and necrotizing, and often complicated by retroperitoneal sepsis. The mortality in necrotizing pancreatitis approaches 50%. Critical care is mandatory in these patients. It ensures early aggressive resuscitation, close monitoring of the patient, and prompt diagnosis and management of complications frequently observed in the fulminant forms of the disease.

ETIOLOGY

The two important causes of acute pancreatitis are gallstone disease and excessive alcohol consumption. Pathogenesis in gallstone disease may be related to obstruction of the pancreatic duct during passage of a gallstone. This obstruction results in ductal hypertension which through rather obscure mechanisms leads to zymogen activation. Activated pancreatic enzymes cause pancreatic inflammation, tissue destruction and various complications observed in the disease.

The pathogenesis of pancreatic inflammation in alcohol abuse, is obscure. Alcohol may have a direct action on acinar cells or may produce spasm of the sphincter of Oddi, with ductal hypertension. Alcohol-induced pancreatitis is directly related to the quantity and duration of alcohol consumption.

Pancreatitis may occasionally follow abdominal surgery, particularly surgery on the biliary tree. Early detection may be difficult, as the clinical features in these patients are often atypical. Persistent pain or unexpected prolonged ileus following abdominal surgery should raise the possibility of pancreatitis.

Box 1: Etiology of acute pancreatitis

- Gallstones
- Alcohol
- Following surgery, especially after biliary tract surgery
- Trauma
- Post-endoscopic retrograde cholangiopancreatography (ERCP)
- Pancreatic tumors
- Drugs—corticosteroids
- Hypercalcemia
- Hyperlipidemia
- Autoimmune pancreatits
- Infections, e.g. mumps, coxsackie virus
- Polyarteritis nodosa and other collagen disorders
- Low flow states/embolic
- Idiopathic

Endoscopic retrograde cholangiopancreatography (ERCP) results in acute pancreatitis in 2% of cases.

There are numerous other causes of pancreatitis listed in Box 1.[1] These include drugs, viral and other infections, trauma, pancreatic tumors, autoimmune disease and metabolic causes (hypercalcemia, hyperlipidemia). Pancreatitis is also associated with Type I and Type V hyperlipoproteinemias. Hypertriglyceridemia may be the underlying mechanism in these patients. Rarely, autoimmune disease can cause or be associated with pancreatitis. In spite of an elaborate work-up, 7–10% of patients have idiopathic pancreatitis, where the cause is undetermined.

Box 2: Important critical illnesses and problems in the ICU that predispose to acute pancreatitis

- Major upper abdominal surgery
- Shock of any etiology
- Cardiopulmonary bypass
- Repair of abdominal aortic aneurysm
- Kidney/liver transplantation

Patients in the ICU with acute pancreatitis, fall into two groups—

1. Those who were in reasonably good health, and who are now stricken with the disease and require intensive care. These patients are admitted primarily for acute severe pancreatitis.
2. Those who are already seriously ill in the ICU with a critical illness, and in whom pancreatitis develops as a further complication. The list of critical illnesses in the ICU that form a background to a complicating pancreatitis continues to grow, and is shown in Box 2.

The reason why seriously ill patients with diverse critical illnesses should develop the unrelated and potentially lethal complication of acute pancreatitis is poorly understood. Multifactorial causes are probably responsible.[1] Review of possible mechanisms of acute pancreatitis in critically ill patients suggests that hypoperfusion injury plays an important pathogenetic role. Warshaw and O'Hara[2] go so far as to suggest that shock from any cause is a risk factor for the development of acute pancreatitis. The mechanisms that relate hypoperfusion states to release of activated pancreatic enzymes, and to pancreatic inflammation, are not known.

PATHOPHYSIOLOGY[3-5]

The pancreas secretes a number of digestive enzymes, which are secreted as inactive proenzymes or zymogens. When activated enzymes come in contact with tissues outside their usual milieu, they have the potential to produce inflammation, necrosis and cellular death. This is normally prevented by the storage of inactive pancreatic zymogens and enzyme activators in separate cytosol granules. Once the integrity of this protective compartmentalization is lost, autodigestion due to enzymatic activation occurs, initiating a self-perpetuating inflammatory reaction. Activated enzymes, which include proteases such as trypsin, chymotrypsin and elastase, can in turn activate proenzymes in the inflammatory and complement cascades. Lipase produces fat necrosis and liberates phospholipid remnants. Inflammation and necrosis is not confined to the pancreatic and peripancreatic area, but can occur in various organ systems, leading to multiple organ dysfunction and death.

Sepsis frequently complicates necrotizing pancreatitis. Systemic toxicity is related to the release of several mediators, including arachidonic acid metabolites, interleukin-1 and other cytokines.

CLINICAL FEATURES AND DIAGNOSTIC EVALUATION[1,4,5]

Clinical assessment is initially directed toward establishing a diagnosis and determining the severity and prognosis of acute pancreatitis. Further diagnostic evaluation is then necessary to identify the presence of pancreatic necrosis and pancreatic and peripancreatic suppuration. The timing and nature of surgical intervention in some of these patients is indeed a matter of fine judgment based on clinical features, results of diagnostic tests, and experience.

Abdominal pain and vomiting are invariably present. Unlike the pain of a perforated peptic ulcer, the severity of which is maximal almost from the start, the pain of acute pancreatitis often builds up to a crescendo over a matter of hours. The pain is classically initially felt in the upper abdomen. It is however often poorly localized, and may be felt all over the abdomen, as also in the back. Rarely, it is experienced more in the back than the abdomen. Low grade fever is often present. Abdominal distension and tenderness on palpation are present, but guarding and rigidity denoting peritonitis, are late in developing and may be absent to start with. Abdominal findings in any case, do not necessarily indicate the severity of the retroperitoneal inflammatory process. Localized ileus may cause gastric dilatation which worsens vomiting. Localized effect of inflammation on the distal transverse colon leads to distension of the loop of the transverse colon with the "colon cut off" sign on X-ray of the abdomen. In fulminant cases when retroperitoneal inflammation extends beyond the pancreas, erythema around the flanks may occur. Ecchymosis of the flanks (Grey-Turner's sign), and of the umbilicus (Cullen's sign), have been described, but are rarely observed. These signs reflect bleeding into the pancreatic bed or retroperitoneal space.

All patients with severe pancreatitis show circulatory changes of hypovolemia, characterized by tachycardia, hypotension, cold peripheries and a falling urine output. Hypovolemia is due to transudation of fluid into the retroperitoneal space, peripancreatic and extrapancreatic tissues, to sequestration of fluid in the ileum and to ascites. In fact, the diagnosis of acute pancreatitis should be always considered in any patient with abdominal pain and a compromised circulation.

Peripancreatic fluid collections occur in up to 50% of patients. Pseudocysts are better defined collections of fluid within the lesser sac, and occur in 10–15% of patients. Pseudocysts can compress the stomach, duodenum and rarely the bile duct. Pseudocysts can leak into the peritoneal cavity, or track into the retroperitoneal space, pleural cavity or even rarely into the pericardial space.

Necrosis of a part of the inflamed pancreas is termed acute necrotizing pancreatitis (Fig. 1). If volume replacement has been adequate, necrotizing pancreatitis is characterized by clinical features of the systemic inflammatory response syndrome and is associated with a hyperdynamic circulation, tachycardia, tachypnea, hypotension and fever.

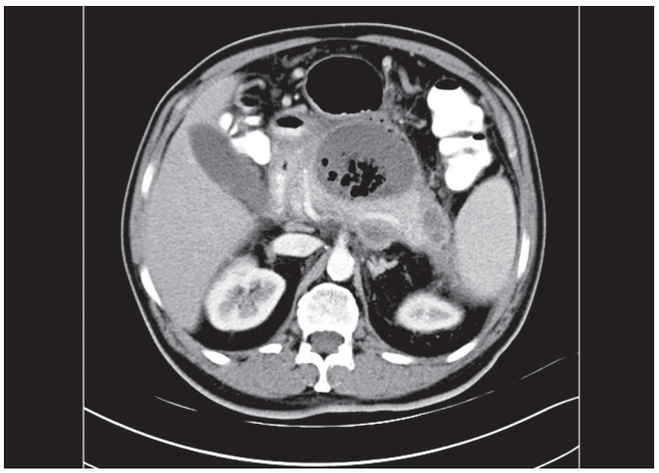

Fig. 1: Acute necrotizing pancreatitis

Pulmonary complications are an intrinsic feature of almost every patient with severe necrotizing pancreatitis. Tachypnea is invariably present. Hypoxia may occur without significant changes in an X-ray of the chest. Raised diaphragms, basal atelectasis are commonly observed. Pleural effusions (usually left sided) are frequent; the pleural fluid is an exudate with high amylase content.

Diagnosis

The diagnosis of acute pancreatitis requires two of the following three features—

1. Abdominal pain consistent with acute pancreatitis.
2. Serum amylase or lipase activity at least three times greater than the upper limit of normal.
3. Characteristic findings on contrast enhanced high resolution computed tomography (HRCT) or trans-abdominal sonography.

If abdominal pain suggests pancreatitis, but amylase and/or lipase levels are not significantly elevated, an HRCT of the abdomen is necessary to confirm the diagnosis. If however abdominal pain consistent with acute pancreatitis is associated with a very significant rise in pancreatic enzymes, an HRCT of the abdomen is not usually required in the emergency department or on admission to the ICU. This investigation then can be done after a few days and will provide more information than when done on admission.

COMPLICATIONS[6,7]

Complications may be local (within the abdomen), or systemic [taking the form of the multiple organ dysfunction syndrome (MODS)]. One should consider complications to be really a progressive evolution of the pathology and natural history of fulminating pancreatitis.

Local Complications

i. Local fluid collections have been already commented upon.
ii. Erosion of mesenteric vessels can lead to massive colonic bleed, to haematemesis, or to severe melaena. Haemorrhage into the pancreas, pancreatic duct or pancreatic bed can also occur (Hemosuccus pancreaticum). Portal vein thrombosis is commonly observed.
iii. Gastric outlet obstruction or biliary obstruction may occur.
iv. Pancreatico-enteric or pancreatico-colonic fistulas may occur.
v. Necrotizing pancreatitis is associated with infection in the necrotic area in about one-third of patients with necrosis, leading to increasing sepsis. Suppuration within the pancreas can lead to a localized abscess (walled off necrosis). Suppuration can also involve the peripancreatic area. Local fluid collections can also suppurate.
vi. The abdominal compartment syndrome may occur with disastrous consequences if increased intra-abdominal pressure is not relieved.

Systemic Complications

Multiple Organ Dysfunction Syndrome[7]

This is the most dreaded and frequent complication of severe necrotizing pancreatitis, particularly if the necrotic areas are infected. All organs can be involved. ARDS occurs in more than 20% of patients and is associated with a mortality of over 60%. Oliguric renal failure is associated with a mortality greater than 50%. Liver cell dysfunction is often observed. Disseminated intravascular coagulopathy has a grim prognosis. Metabolic complications include hyperlipidaemia, hyperglycaemia, hypocalcaemia and metabolic acidosis. Rarely coma results from a pancreatic encephalopathy.

In critically ill patients already under intensive care, the sudden added complication of acute pancreatitis may go unrecognized for a length of time. Abdominal pain and vomiting may not be severe enough to draw attention to the nature of the problem. The patient may develop non-specific features of fever, leukocytosis, haemodynamic instability, and hypotension necessitating increased fluid requirements. Yet, the classic major abdominal signs may be still absent. A quick deterioration in an already ill individual is observed. Diagnosis is possible only if there is a high index of suspicion.

Severe pancreatitis may be clinically difficult to distinguish from perforation, bowel obstruction, bowel infarction, and a leaking abdominal aortic aneurysm. Each one of these pathologies, except acute pancreatitis, requires immediate surgical intervention. The importance of a correct diagnosis can therefore never be overstressed.

LABORATORY INVESTIGATIONS[1,8]

Elevated serum amylase and lipase levels are found in a number of patients, but these tests lack both good sensitivity and specificity. A normal serum amylase does not exclude

Table 1: Ranson's early objective prognostic signs used for estimating risk of death or major complications in acute pancreatitis

On admission	*During first 48 hours*
Age >55	Hematocrit fall >10 percentage points
WBC >16000/mm^3	BUN rise >5 mg/100 mL
Blood sugar >200 mg/100 mL	Serum calcium <8 mg/100 mL
Serum LDH >350 IU/L	PaO_2 <60 mm Hg
SGOT >250 U/dL	Base Deficit >4 mEq/L
	Estimated fluid sequestration >6 L

Abbreviations: WBC, white blood cells; LDH, lactate dehydrogenase; SGOT, serum glutamic oxaloacetic transaminase; BUN, blood urea nitrogen.
Source: Ranson JH, Rifkind KM, Turner JW. Prognostic signs and non-operative peritoneal lavage in acute pancreatitis. Surg Gynecol Obstet (now called J of Am College of Surgeon). 1976;143(2):209-19.

acute pancreatitis, and enzyme elevation is often also observed in a perforated ulcer, postoperative states, bowel obstruction and infarction, renal insufficiency and ruptured ectopic pregnancy. Serum amylase levels greater than 1,000 Somogyi units are however most frequently observed only in acute pancreatitis. The measurements of isoenzymes of amylase lend some further specificity to elevated amylase levels, but the sensitivity is not what it should be. Amylase levels in blood may fall to normal within a few days after pancreatitis. Serum lipase levels remain elevated for 7–10 days; lipase activity is perhaps more sensitive and specific compared to amylase activity. Elevated lipase levels have been reported in bowel obstruction and cholecystitis.

Patients with gallstone pancreatitis have generally much higher aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase levels, compared to pancreatitis due to other etiologies.

Other routine blood and biochemical tests are done as for any patient with a serious illness; none of these are diagnostic. A low serum calcium level is often observed. Arterial pH for determining metabolic acidosis and arterial blood gases should always be estimated.

Patients presenting with suspected acute pancreatitis should undergo routine abdominal and chest X-rays, which help in differentiating pancreatitis from intestinal obstruction and perforation. Pleural effusions in a patient with severe abdominal pain should suggest pancreatitis. Pancreatitis may also be suggested by localized jejunal or colonic ileus, a widened duodenal C loop, associated radio-opaque gallstones, free fluid within the abdomen, and gas in the pancreatic bed, suggestive of a pancreatic or peripancreatic abscess.

IMAGING STUDIES

Imaging the pancreas by ultrasound[9] and CT scan studies[10] are far more sensitive diagnostic tests than the serial estimation of enzyme levels in blood. Demonstration of an enlarged pancreas by imaging techniques confirms a diagnosis. Imaging abnormalities, even in mild cases, often persist for 1 week so that this modality is useful for the retrospective diagnosis of acute pancreatitis. Both ultrasound and CT imaging should be used, as they are complimentary to each other. The presence of bowel gas or obesity interferes with the examination of the retroperitoneum by ultrasonography. Subtle changes in tissue density denoting necrosis, hemorrhage and suppuration are not easily defined by this imaging technique. However, valuable information about the biliary tree can be obtained, and ultrasonography has more sensitivity than the CT scan in picking up stones obstructing the biliary tree. CT scanning is invaluable for a study of the retroperitoneal space. Its crucial value lies in the recognition and follow-up of local complications of acute pancreatitis. It thus identifies pancreatic necrosis, hemorrhage and pancreatic and peri-pancreatic suppuration with precision.[10] It is also superior to ultrasonography in identifying high density fluid collections in the transverse mesocolon, small bowel mesentery, pararenal, perirenal, renal and paracolic spaces (see Section Imaging in the Critical Care Unit).

SEVERITY OF DISEASE

It is important for the critical care physician not only to establish a diagnosis of acute pancreatitis but also to assess its severity. Ranson's criteria[11] have been used since 1976 to assess the severity and prognosis of a patient who presents with, and is admitted for acute pancreatitis. These criteria are difficult to evaluate in a patient who is already critically ill and who then develops pancreatitis as an added complication. Many of Ranson's criteria are directed towards the systemic effects of the disease. In patients who are critically ill to start with, many of these criteria may already be present prior to the onset of pancreatitis. They are therefore of little value in assessing the prognosis and severity of the disease under the circumstances stated above. Table 1 lists Ranson's diagnostic criteria.

The acute physiology and chronic health evaluation II (APACHE II) scoring system has also been used to assess the severity and prognosis of acute pancreatitis.[12] Increased APACHE II scores correlate with increased risk of inhospital mortality, but lack sensitivity in determining acute severe pancreatitis.

Current severity indices are based on clinical and imaging findings. The severity is determined by severe persistent pain, organ failure lasting more than 48 hours. Renal failure and respiratory failure indicate severe disease.

A new bedside scoring system, the bedside index for severity in acute pancreatitis (BISAP)[12,13] (Box 3) identifies patients at a high risk of death and is probably as good as the more detailed scoring systems devised to assess disease severity.[14] The BISAP system assigns one point for each of the following signs within 24 hours of presentation.

Blood urea nitrogen (BUN) greater than 25 mg/dL, impaired mental state, systemic inflammatory response syndrome (SIRS), age greater than 60 years and pleural effusion.

Box 3: Individual components of the BISAP scoring system

BUN >25 mg/dL
Impaired mental status (Glasgow Coma Scale Score <15)
SIRS; SIRS is defined as two or more of the following—
1. Temperature of <36°C or >38°C
2. Respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg
3. Pulse >90 beats/min
4. WBC <4,000 or >12,000 cells/mm^3 or >10% immature bands
Age >60 years
Pleural effusion detected on imaging

Abbreviations: BUN, blood urea nitrogen; SIRS, systemic inflammatory response syndrome; WBC, white blood cells.

Table 2: Severity grading based on CT

Grade of acute pancreatitis based on non-contrast CT findings	Points (A)
A. Normal pancreas	0
B. Pancreatic enlargement	1
C. Pancreatic or peripancreatic fat inflammation	2
D. Single peripancreatic fluid collection	3
E. Two or more fluid collections and/or retroperitoneal air	4
Degree of pancreatic necrosis based on contrast CT findings	**Points (B)**
A. No pancreatic necrosis	0
B. Up to 30% of the gland	2
C. 30%-50% of the gland	4
D. >50% of the gland	6
CT severity index (CTSI)	**A + B**
Mild pancreatitis	0–2
Moderate pancreatitis	3–6
Severe pancreatitis	7–10

A BISAP score greater than 3 denotes severe disease with an increased risk of complications.

The above score is to be calculated within 24 hours. A score of one is given to each of the above criteria if present. As mentioned earlier, a score greater than 3 calculated within 24 hours of presentation denotes severe disease with increased risk of complications.

The CT severity index (CTSI) is another scoring system (Table 2). It is based on CT grading (A-E) and percent of necrosis.[10,14]

The scoring systems described above in our opinion are either cumbersome or fail to take into account the changing clinical features with the evolution of the disease. The difficulties with these scoring systems led to a revised classification adopted at the recent Atlanta International Symposium held in 2012. This revised Atlanta Classification classifies fluid collections in acute pancreatitis as also the degree or severity of acute pancreatitis.[10]

Table 3: Revised Atlanta classification of fluid collections in acute pancreatitis[10]

<4 Weeks after onset	
Type of pancreatitis	*Fluid collection*
IEP	APFC • Sterile • Infected
Necrotizing pancreatitis	ANC Parenchymal necrosis alone • Sterile • Infected Peripancreatic necrosis alone • Sterile • Infected Pancreatic and Peripancreatic necrosis alone • Sterile • Infected
≥4 Weeks after onset	
Type of pancreatitis	*Fluid collection*
IEP	Pancreatic pseudocyst • Sterile • Infected
Necrotizing pancreatitis	WON • Sterile • Infected

Abbreviations: IEP, interstitial edematous pancreatitis; ANC, acute necrotic collection; APFC, acute peripancreatic fluid collection; WON, walled-off necrosis.

CRITICAL APPRECIATION OF SEVERITY GRADING OF ACUTE PANCREATITIS

The different severity scoring systems in acute pancreatitis appear to me as an organized attempt by various scientific bodies to confuse the reader! Ranson's early objective prognostic signs estimating risk of death or major complications in acute pancreatitis , as also the bedside index for severity in acute pancreatitis (BISAP) may not be very accurate but atleast can be lauded for their simplicity. No classification of acute pancreatitis can be perfect but the most recent revised Atlanta classification given below is commendable both for its simplicity, its brevity and its holistic approach to a difficult problem.

The revised current (2012) Atlanta classification[15] of acute pancreatitis suggests that the disease has two phases, early and late.

To start with, it defined three types of acute pancreatitis, interstitial edematous pancreatitis, necrotizing pancreatitis and infected pancreatic necrosis (Table 3). Severity is classified as mild, moderate and severe (Box 4).

Mild acute pancreatitis is the most common form; it exhibits neither organ failure nor any local or systemic complications; and usually responds within the first week.

Box 4: Grades of severity of acute pancreatitis according to the Revised Atlanta Classification[10]

Grades of severity

- Mild acute pancreatitis—
  - No organ failure
  - No local or systemic complications
- Moderately severe acute pancreatitis—
  - Organ failure that resolves within 48 h (transient organ failure) and/or
  - Local or systemic complications without persistent organ failure
- Severe acute pancreatitis—
  - Persistent organ failure (>48 hour)—
    - » Single organ failure
    - » Multiple organ failure

Abbreviations: BUN, blood urea nitrogen; SIRS, systemic inflammatory response syndrome; WBC, white blood cells.

Moderately severe acute pancreatitis is defined by the presence of transient (<48 hours) organ failure, local complications, or exacerbation of comorbid disease.

Severe acute pancreatitis is characterized by persistent organ failure, that is organ failure lasting more than 48 hours. Three organ systems should be assessed to define organ failure, respiratory, cardiovascular and renal. Organ failure is defined as a score of 2 or more for one of these organ systems using the Marshall Scoring System.[15]

Local complications are peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst and walled off necrosis (sterile or infected).

The current classification also gave a standard template for reporting CT images.

IDENTIFICATION OF LOCAL PANCREATIC COMPLICATIONS

In a patient who progressively deteriorates, or who after a phase of significant improvement lasting from 8-10 days, again starts to deteriorate, pancreatic complications should always be suspected. These fortunately can be proven by the CT appearance of increasing pancreatic necrosis complicated often by infection of the necrotic area. CT guided percutaneous needle aspiration of areas of pancreatic necrosis or of pancreatic and parapancreatic fluid collections has been the standard recommended approach for the presence or absence of infection in these necrotic areas. Microscopic examination with Gram stain and culture of aspirated material for aerobic and anaerobic organisms should be done.[16,17] At least 30–40% of necrotic collections are found to be infected. Gram-negative infections particularly due to *E. coli*, *Klebsiella* and *P. aeruginosa* are most frequent. However, a wide variety of Gram-positive and Gram-negative organisms, both aerobic and anaerobic, and occasionally fungi have been isolated on culture.

Currently, particularly in specialized centers, CT guided diagnostic aspiration is infrequently performed. This is because of the dictum (elaborated upon later) that any operative interference in acute pancreatitis as far as possible is best avoided for at least 4 weeks after the onset of the disease. If after this period, operative interference through minimally invasive techniques is felt to be necessary, tissue for culture can be effectively taken at that point in time. Perhaps the only advantage of an earlier CT guided biopsy in a patient suspected to have an infected pancreatic or peripancreatic necrosis is to help identify an organism which necessitates a change in antibiotic or antifungal therapy

EVALUATION OF OTHER ORGAN SYSTEMS

Acute necrotizing pancreatitis is an important cause of MODS. Each organ system therefore needs careful evaluation and daily follow-up both through clinical examination and relevant laboratory tests. Involvement of the respiratory system is part and parcel of the features of severe pancreatitis. Hypoxic respiratory failure may occur without ARDS. A CT scan of the lower chest often shows presence of pulmonary involvement which has been undetected on a chest X-ray.

The evolution of ARDS is characterized by an increasing alveolar-arterial gradient, bilateral pulmonary shadows and an increasing right to left shunt within the lungs.

Renal function, liver function, metabolic abnormalities, arterial pH and blood gas changes, central nervous system (CNS) function and alteration in the coagulation profile need careful evaluation.

The numerous possible complications of fulminant pancreatitis are given in Box 5.

MANAGEMENT[1,6]

Management requires the presence of a team consisting of the critical care physician, an interventional gastroenterologist, a surgeon experienced in pancreatic surgery and a radiologist. Other specialities may need to be involved. However, management should be coordinated by a single individual who looks at the overall problem in its entirety and not solely on individual disordered organ systems.

Management includes—

- Careful monitoring of the patient.
- Relief of pain.
- Correction of hemodynamic defects, chiefly correction of volume depletion and electrolyte abnormalities. It is essential to maintain adequate oxygen transport and tissue perfusion to important organ systems during the period of acute illness, and during resolution of the inflammatory process within the pancreas.
- Correction of metabolic abnormalities.
- Control of pancreatic enzyme secretion as far as possible.
- Support to all other organ systems, particularly the respiratory and renal systems.
- Nutritional support.

Box 5: Complications of acute (fulminant) pancreatitis

A. Local—
- Pancreatic/peripancreatic suppuration and necrosis
- Pancreatic abscess
- Pseudocyst formation
- Portal vein and other venous thrombosis
- Gastric outlet obstruction and/or biliary obstruction
- Enteric fistulae
- Catastrophic GI bleeds or bleeding into retroperitoneal tissues due to pancreatic/peripancreatic inflammation destroying vessel walls, or causing erosion of splenic or other large vessels

B. Systemic—
- Multiple organ dysfunction and failure
- Respiratory - Pleural effusion, V/Q abnormalities, acute lung injury
- Renal dysfunction
- Hepatic dysfunction
- Metabolic acidosis
- Electrolyte abnormalities
- Coagulopathy
- CNS—Pancreatic encephalopathy

Abbreviations: GI, gastrointestinal; V/Q, ventilation/perfusion; CNS, central nervous system.

- Use of antibiotics.
- Treatment of local complications arising from acute pancreatitis.

Ongoing evaluation of the patient requires close cooperation between the physician and a surgeon experienced in the surgical management of abdominal complications. The decision regarding the timing and nature of the surgical intervention is based not only on the clinical features, biochemical investigations, and CT appearances, but also on clinical experience and judgment.

Careful Monitoring of the Patient

In critically ill patients, full hemodynamic monitoring is of great value, and should include heart rate, arterial blood pressure, ECG, central venous pressure, and hourly urine output. In patients with large volume deficits, or in those who are hemodynamically unstable, or have sepsis or pulmonary complications, a Swan-Ganz catheter may be necessary to measure and monitor pulmonary capillary wedge pressure, cardiac index, vascular resistances and oxygen derived variables.

Frequent examination of the complete blood count (CBC), blood chemistry, serum electrolytes and arterial blood gases are necessary to detect complications, to evaluate the function of various organ systems, and to judge the adequacy of treatment.

Serial ultrasounds and CT scans are of great importance in evaluating retroperitoneal complications.

Relief of Pain

Pain can be excruciating in the early phase. Pethidine 25 mg intravenously or 100 mg intramuscularly is preferred to morphine, as the latter can contract the sphincter of Oddi, and can theoretically worsen the pancreatitis. Buprenorphine 150 µg diluted in 10–20 mL of N saline and given slowly 8 hourly via an epidural catheter, is also effective in relieving pancreatic pain. When severe pain persists in spite of the above analgesics, epidural anaesthesia prompts quick relief, allows the patient to breathe far more comfortably and reduces the incidence of basal atelectasis so frequently observed in these patients.

Fluid and Electrolyte Restitution and Correction of Hemodynamic Defects

Volume replacement is of crucial importance. *Acute fulminant pancreatitis is in effect a massive retroperitoneal burn with an ongoing loss of fluid into the retroperitoneum, peritoneal cavity, and into the gut.* Volume requirements vary. In severe cases it may be more than 8–10 L within a period of 24 hours. The adequacy of fluid replacement in severe cases should be judged clinically, by monitoring the central venous pressure and in complicated problems the pulmonary capillary wedge pressure. The latter should be kept between 12–15 mm Hg. Fluids used for volume replacement include both colloids (IV albumin) and isotonic crystalloids. The use of the pulmonary artery catheter has its inherent risks and should be reserved for special problems as in elderly patients, patients with myocardial dysfunction and patients who manifest pulmonary congestion early during fluid replacement therapy.

It is essential to remember that *though early fluid resuscitation is important, over-vigorous replenishment of fluid predisposes to ARDS and may thereby increase the mortality in the disease.*

Potassium replacement is also invariably necessary. Blood transfusions may be necessary to counter retroperitoneal hemorrhage produced by proteolytic enzyme extravasation. Hypoalbuminemia when present, should be treated by intravenous infusions of albumin. Successful fluid resuscitation should result in warm peripheries, a good pulse volume, a normal arterial blood pressure, a good urine output and an improved mixed venous oxygen tension (PvO_2) or an improved saturation of blood in the superior vena cava.

If the patient is still hypotensive in spite of adequate fluid replacement [as judged by the central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP)], inotropic and/or vasopressor suport is mandatory. Dopamine 10–15 µg/kg per minute in a slow intravenous infusion, offers good cardiovascular support. Dobutamine may be preferred to dopamine in patients who are already vasoconstricted. Both these drugs can be used for inotropic support. Norepinephrine at 5-20µg/kg per minute may also need to given as vasopressor support. It is important to optimize oxygen delivery or transport, in the hope that perfusion improves, and oxygen uptake and oxygen utilization by tissues are increased.

Evaluation of organ perfusion is difficult. Perfusion of tissues may be inadequate even in the presence of a normal arterial blood pressure. A low PvO_2 (<35 mm Hg), and/or the presence of lactic acid acidosis, are additional pointers to hypoperfusion.

Correction of Metabolic Abnormalities

Metabolic acidosis, hyperglycemia, hypokalemia, hyperkalemia, hypocalcemia and hypomagnesemia must be recognized and treated. Restoration of fluid volume, arterial blood pressure and perfusion, generally suffice to correct the metabolic acidosis.

Control of Pancreatic Enzyme Secretion

There is no definite way of reducing pancreatic enzyme secretion in acute pancreatitis. Nasogastric suction is advisable in severe cases; it is absolutely indicated in the presence of ileus and continuous vomiting. It decreases the risk of aspiration, and may perhaps help in reducing pancreatic secretions. A H_2-antagonist or proton pump inhibitor is used intravenously to help reduce gastric acid secretion. This decreases the chances of bleeding from acute erosions, and may perhaps also help to reduce pancreatic secretions. Somatostatin in an intravenous bolus dose of 500 µg, followed by an infusion of 250 µg over 4 hours, has also been shown to suppress pancreatic secretion. However, its high cost precludes its use for many patients in our part of the world. Octreotide in a dose of 50 µg three times daily subcutaneously can be used in place of somatostatin to help reduce pancreatic secretions.

Support to Other Organ Systems

Acute pancreatitis is an important cause of multiorgan failure. Support to all failing organs is necessary.

Cardiorespiratory Support

Patients who are severely tachypnoeic with a respiratory rate greater than 35/minute, or who have a PaO_2 less than 60 mm Hg in spite of getting oxygen at 6-8 L/minute through nasal prongs or a face mask, need to be intubated and kept on ventilator support. Mechanical ventilation ensures a high PaO_2 and maximum oxygen saturation of arterial blood. The evolution of acute lung injury and ARDS requires expert ventilatory care till such time as the complication resolves. *Increased alveolar-arterial oxygen gradients with a low PaO_2 may occur in pancreatitis, without necessarily progressing to ARDS*. Support to the cardiovascular system has already been detailed earlier.

Renal Support

Renal function may deteriorate despite adequate haemodynamic resuscitation. In patients with increasing azotaemia, temporary haemodialysis or haemofiltration should be carried out till renal function returns. Recovery following a complicating acute tubular necrosis is possible with good critical care.

Correction of metabolic abnormalities and maximal support to all organ systems, such as the liver and hematological systems is mandatory.

Nutritional Support[18]

All oral feeds or nutrients are stopped in severe pancreatitis as pancreatic exocrine secretion is stimulated by intragastric and intraduodenal stimuli. The first priority is the restitution of fluid and electrolyte loss and restoration of hemodynamic stability. Once this is achieved patients are started on nutritional support. The recent trend is to use total enteral nutrition (TEN) through a naso-jejunal tube. It has been shown that early use of the gut maintains mucosal integrity and prevents translocation of intestinal bacteria into the pancreatic bed, thereby reducing the incidence of pancreatic infection, an important cause of morbidity and mortality in this disease.

Ideally the patient should be maintained in a positive nitrogen balance, though this may at times prove impossibly difficult. A total caloric intake of 25–30 kcal/kg should suffice. Proteins should supply 1–1.25 g/kg and 50–60% of the nutrient mixture should consist of carbohydrate. Hyperglycemia should be controlled by insulin so that blood sugar levels are not greater than 150 mg/dL. In patients fed enterally, a low fat diet, with fats constituting less than 20% of total calories is preferable as this minimizes pancreatic stimulation. Elemental diets that contain fat in the form of medium chain triglycerides should be used to minimize pancreatic stimulation.

Enteral nutrition may be impossible in the presence of fulminating disease associated with vomiting, distension, ileus, peritonitis and severe sepsis. In these patients nutritional support with caloric intake outlined above should be given by total parenteral nutrition. Intravenous lipid emulsions are not harmful in patients with severe pancreatitis. Nosocomial sepsis through central catheter-related infections are a grave potential danger in patients on parenteral nutrition.

Vitamins, minerals, calcium, magnesium, antioxidants also need to be given for nutritional support.

Criteria for starting oral feeds are—(i) sharp reduction or absence of abdominal pain; (ii) reduction of amylase and lipase to near normal levels; (iii) absence of complications like pancreatic fistulas and (iv) resolution of ileus with return of bowel sounds.

Antibiotics

The early stage of acute pancreatitis does not warrant the use of antibiotics. Fever at this stage is due to the systemic inflammatory response syndrome. The fever generally settles down or is low-grade after a week. If fever and clinical features return, the possibility of pancreatic necrosis and supervening infection should prompt the empiric use of antibiotics. Imipenem and meropenem are antibiotics with a good penetration into pancreatic tissue and are often used in combination with metronidazole. If the possibility of an associated fungal infection is entertained (depending on risk

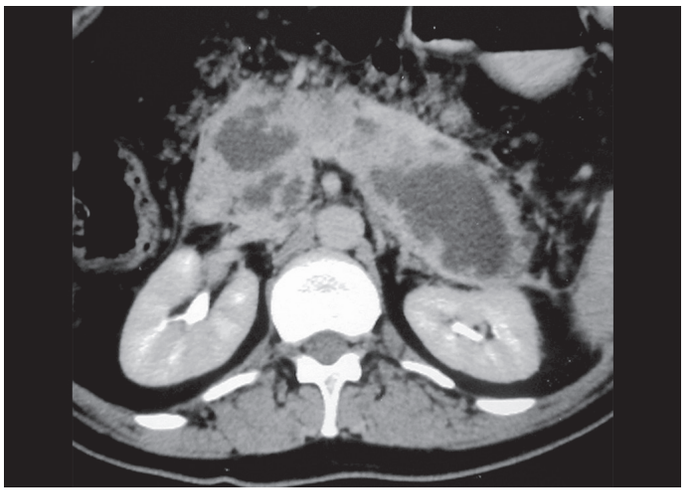

Fig. 2: Pancreatic necrosis: CT scan reveals multiple areas of necrosis in the head and body of the pancreas representing pancreatic necrosis

factors) in a given patient, antifungals may also need to be used empirically

Critical Care Management of Complications of Pancreatitis[14]

The complications that should be anticipated are—(i) pancreatic necrosis; (ii) infected necrosis, pancreatic abscess and peripancreatic suppuration; (iii) pseudocyst formation. Other complications include (iv) enteric fistulae and (v) catastrophic bleeds.

Pancreatic Necrosis

Patchy devitalization with necrosis of the pancreatic gland occurs from within a few days to a few weeks of the onset of acute inflammation. The clinical picture is one of persistent low grade fever, abdominal pain and leukocytosis. The diagnosis is made on a CT scan which shows local areas of nonenhancement. It may be impossible to determine whether the necrotic area is infected or not. A CT-guided needle aspiration with microbiological examination of the aspirate is the only method to determine whether the necrotic area is infected. The growth of aerobic and/or anaerobic organisms signifies infection. A negative culture however, does not always exclude the presence of infection in a necrotic area. Only 30–40% of patients with pancreatic necrosis get infected. Surgery should not be done if the patient has only a low grade fever, the CT findings are not suggestive of an infected necrosis or abscess, and if a CT guided aspiration of the necrotic is sterile (Fig. 2) (see later discussion on surgery).

Infected Pancreatic and Peripancreatic Necrosis, Pancreatic Abscess

Contamination of the necrotic pancreas by bacteria (presumably from the transverse colon) leads to infected pancreatic necrosis. Liquefaction of the necrotic areas produces an abscess which can be generally made out on a CT scan. CT-guided needle aspiration is positive for bacteria on Gram stain and/or a culture. The clinical course in patients with retroperitoneal sepsis can be rapidly downhill, with spiking fever, leukocytosis, tachycardia and tachypnea.

Surgical Intervention in Infected Pancreatic and/or Peripancreatic Necrosis The mortality in patients from infected pancreatic necrosis is 15–40%.[19] Death in the majority of these patients is due to fulminant sepsis with progressive multiple organ dysfunction syndrome. Surgery in fulminant necrotizing pancreatitis should be reserved only for pancreatic sepsis. However, early endoscopic retrograde cholangiopancreatography (ERCP) within 48–72 hours of the onset followed by laproscopic cholecystectomy should be performed in patients with suspected biliary calculi with or without cholangitis. ERCP along with a sphincterotomy is indicated if there is persistent hyperbilirubinemia of greater than 3 mg/dL, or a suspicion of cholangiolitic abscesses as judged by fever with chills and hyperbilirubinemia. MRCP imaging usually helps to detect an impacted stone in the bile duct.

Currently, experience of several surgeons in the field of pancreatic surgery has led to the following guidelines for surgical intervention in necrotizing pancreatitis.[20]

A. When should the surgeon intervene?

1. Surgical intervention should be reserved for infected pancreatic and/or peripancreatic necrosis.
2. Surgical intervention if thought necessary should be delayed for at least 4 weeks after the onset of acute pancreatitis. Earlier surgical intervention (i.e. within the first few weeks) is associated with a forbiddingly high mortality. One reason for this is because poorly organized necrosis (present in the early weeks of the disease) is more difficult to manage by any method than partially liquefied and walled off necrosis generally present after 4 weeks of the disease). However, prolonging surgical intervention when indicated well after 4 weeks may worsen sepsis beyond the point of no return.

   Rarely, earlier intervention (earlier than 4 weeks) is required in patients showing sharp clinical deterioration with rapidly progressive multiorgan failure in spite of maximal medical support, especially in those with obstruction of a viscus. The mortality in these patients is however extremely high.
3. Specific scenarios, such as the abdominal compartment syndrome or a perforated viscus, require urgent intervention but not necrosectomy.

B. What form should surgical intervention take?

The traditional approach has been open surgical necrosectomy. The current trend is to avoid open surgery and resort to minimally invasive techniques provided the necessary expertise is available.

Percutaneous catheter drainage, endoscopic, laparoscopic and rigid videoscopic methods are the accepted minimally invasive approaches for treating infected necrosis.

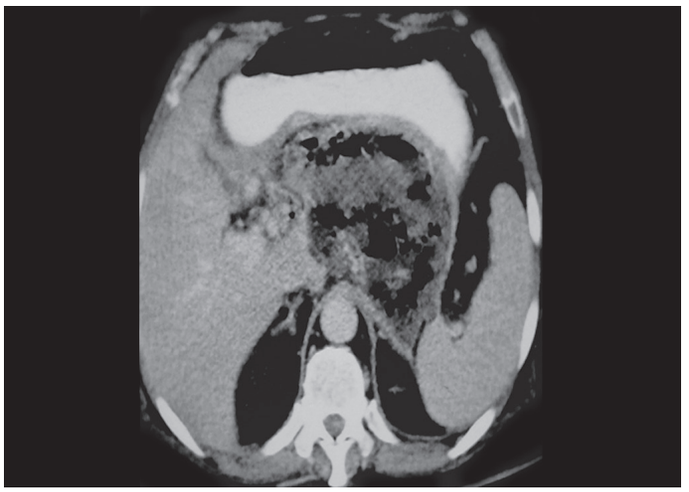

Fig. 3: Pancreatic sepsis: CT scan shows large lesser sac fluid collections with evidence of air within representing pancreatic sepsis

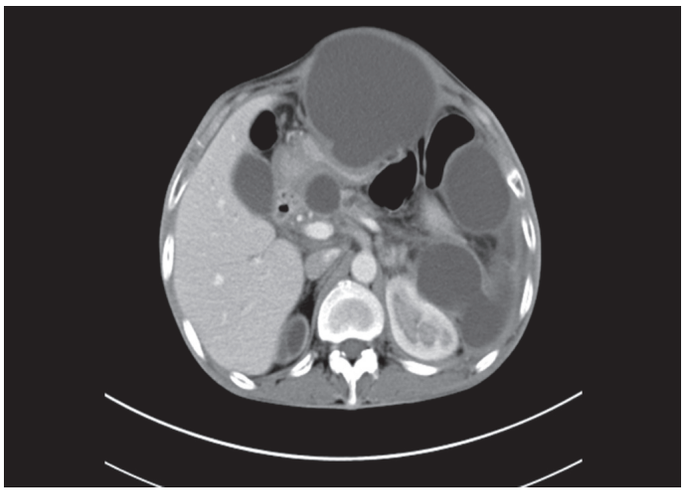

Fig. 4: Pancreatic pseudocyst: CT scan shows multiple well-defined homogenous fluid density lesions in the abdomen representing pseudocysts

The Step-up approach involves percutaneous catheter drainage followed by the minimally invasive approaches for necrosectomy mentioned above. Some patients may recover with just percutaneous drainage and may not require any further surgical intervention. Open surgical necrosectomy should remain an option only in a few selected patients. In a multicenter randomized controlled trial , the short-term and long-term results following the step-up approach has been shown to be superior to immediate open surgery in patients with infected necrosis.[21] However, no single approach is optimal for all patients. The approach is often multimodal and needs to be tailored to the requirement of an individual patient.

Critical care with maximal support is vital in all patients undergoing surgical intervention (Fig. 3).

Pancreatic Pseudocyst[14]

Fluid collections within and around the lesser sac are easily picked up by ultrasound and CT examinations of the abdomen. When sufficiently large, these collections can be palpated per abdomen. Diagnosis of a pancreatic pseudocyst does not necessitate treatment unless the cyst is infected, bleeds or ruptures into the peritoneal cavity or bowel. Repeated percutaneous aspirations of the pseudocyst may however be necessary. Definitive surgery, even for a large pseudocyst, should be delayed preferably for at least six weeks, by which time the patient is stable, and the cyst wall is thick enough to allow anastomosis between the cyst and the gut (Fig. 4).

Enteric Fistula

These occur during the phase of severe retroperitoneal inflammation associated with fulminant pancreatitis. The retroperitoneal inflammation can cause thrombosis of vessels supplying the gut; the middle colic vessels supplying the transverse colon are particularly vulnerable. Necrosis of the colonic wall leads to colonic fistula. Gastric, duodenal and small bowel perforation and fistulae can also occur. Awareness of a possibility of enteric fistulae as a major hazard of acute pancreatitis allows a quicker diagnosis and planned surgical treatment.

Catastrophic Bleeding

Severe bleeding occurs when pancreatic and peripancreatic inflammation destroys vessel walls within the retroperitoneal space or causes erosion of the splenic or other large vessels. Surgical control of bleeding may be virtually impossible in the midst of inflamed distorted tissue planes. Embolization of the vessels employing angiographic techniques to identify the bleeding vessels is the treatment of choice. Ischemic necrosis of the transverse colon can also cause bleeds into the large bowel.

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CHAPTER 56

Acute Gastrointestinal Bleeding

INTRODUCTION

Gastrointestinal (GI) bleeds can occur from any part of the GI tract. Till recently, GI hemorrhage was classified into upper GI bleeds if the bleeding was proximal to the ligament of Treitz and lower GI bleed if the source of bleed was distal to the ligament of Treitz. The development of new strategic therapies has now led to proposals for a new classification. Bleeding originating from the small bowel is considered a separate entity[1,2] and the term lower GI hemorrhage is confined to bleeding from the cecum, colon and/or rectum.

Gastrointestinal bleeding is, therefore, best classified as under—

- Upper GI bleeding—source of bleeding proximal to the ligament of Treitz.
- Small bowel bleeding.
- Lower GI bleeding—source from cecum, colon and/or rectum.

EPIDEMIOLOGY

Upper GI bleeding is about five times more frequent than lower GI bleeding.[2] In the West, GI hemorrhage is more common in the elderly; the reported incidence in this population is as high as 500 cases per 100,000 people per year. The epidemiology in India and other developing countries is not well-established. Demographic trends in India as in the West also show a rising number of elderly patients in the general population. It is therefore likely that both in India and the West, the incidence of GI hemorrhage will steadily rise in the years to come.

Upper GI bleeds, in general, are more severe than lower GI bleeds and more likely to result in shock.[1] Epidemiological studies in the West have shown that despite improvement in management and therapeutic strategies, mortality has remained constant over the last 60 years.[3,4] The persistence of mortality is related to an elderly population, which has many associated comorbidities.[5,6] The high death rate is believed to be independent of GI bleeding, mortality being related to other factors.

UPPER GASTROINTESTINAL BLEEDING

General Considerations

Upper GI bleeds are a frequent cause of emergency admission to hospitals. Upper GI bleeding means bleeding from the esophagus, stomach or duodenum, arising from above the ligament of Treitz. Occasionally, blood arising from the nose, oropharynx, larynx or lungs is swallowed and either vomited as hematemesis or passed through the rectum as maelena. A careful examination and relevant investigations should distinguish such spurious GI bleeds.

Not all patients with GI bleeds require critical care. In at least 75–80% of patients, bleeding stops spontaneously and does not recur. However, about 20% of patients do not stop bleeding, or have a recurrent bleed. It is indeed difficult to predict which patient will continue to bleed or will have a recurrent hemorrhage. Intensive care is indicated in all severe bleeds, bleeds that continue or recur, bleeds in patients with cirrhosis of the liver, in elderly patients, in patients with serious background diseases, for example, ischemic heart disease, or renal failure.

Major Causes of Upper Gastrointestinal Bleed[1-3]

More than 70% of upper GI bleeds are due to acid-peptic disease—duodenal or gastric ulcer, gastric or duodenal erosions, stress ulcers or reflux esophagitis. About 15% of

Box 1: Important causes of upper gastrointestinal bleeds commonly encountered in the intensive care unit

- Acid-peptic disease—duodenal and gastric ulcers, erosions, stress ulcers, reflux esophagitis
- Portal hypertension—esophageal or gastric varices, gastropathy
- Mallory-Weiss tear
- Vascular abnormalities in the upper gastrointestinal tract, e.g. Osler-Weber-Rendu disease
- Carcinoma of stomach/esophagus
- Rarely acute pancreatitis, blood dyscrasias, or coagulation defects

upper GI bleeds are due to esophageal or gastric varices or a gastropathy caused by portal hypertension. The remaining 10–15% of bleeds are due to various etiologies. These include the Mallory-Weiss syndrome, cancer of the esophagus or stomach, vascular anomalies of the upper GI tract (e.g. Osler-Weber-Rendu disease). Acute pancreatitis may occasionally present as an acute severe GI bleed. Rarely a blood dyscrasia or a coagulation defect may present as a GI bleed.

The important causes of an upper GI bleed are listed in Box 1.

Clinical Manifestations

Bleeding from the upper GI tract, from a lesion at or above the ligament of Treitz manifests in one or more of the following ways—

- Hematemesis, which is the vomiting of fresh blood or of altered coffee ground blood.
- Maelena, which is the passage of altered blood in the form of tarry black stools. It must, however, be stressed that, in massive upper GI bleeds, maroon or bright red blood may be passed from the rectum, mimicking a bleed from the small bowel (usually ileum) or colon. Fresh blood from the rectum due to an upper GI bleed is, however, invariably associated with shock and hemodynamic instability.
- The presence of fresh blood or altered blood in the nasogastric aspirate. This may be observed—(1) when an upper GI bleed complicates a separate critical illness for which the patient is under intensive care; (2) when a patient is admitted for shock related to a GI bleed, but which, till the time of admission, has not resulted in hematemesis or maelena.
- Major bleeding in rare instances may not be easily evident, particularly in older patients. Syncope, dizzy spells, unstable angina, undue breathlessness on exertion and increasing pallor may be the initial outward manifestations of a bleed. Confusion and focal neurological signs suggesting transient ischemic attacks may occur in those with cerebrovascular disease. Rectal examination in these old patients may reveal the presence of maelena.

The manifestations of blood loss in upper GI bleeds depend on the degree and rapidity of blood loss. Hypovolemic and hemorrhagic shock have been discussed at length in the Section Clinical Shock Syndromes.

Clinical Approach to an Upper Gastrointestinal Bleed

The fundamental clinical approach should consider the following features—

- Determine the severity of the bleed and assess its effect on the hemodynamics of the circulation, and immediately initiate resuscitation by fluid replacement and transfusions in patients with moderate to severe blood loss.
- Identify high-risk patients.
- Determine the cause of the bleed by appropriate investigations and diagnostic steps. It is of interest that diagnostic procedures and therapeutic strategies are often simultaneously performed in the management of GI bleeds.

Assessment of Severity of Bleed

This has been discussed in the Section Clinical Shock Syndromes. As has been emphasized earlier, changes in pulse rate, blood pressure, skin temperature, urine output, arterial pH are all of help in estimating the degree of blood loss. Some assessment of the severity of the hemorrhage can also be made by examination of the vomitus, nasogastric aspirate and the degree of maelena. Passage of fresh blood from the rectum in an upper GI bleed always signals a massive bleed. Continuous aspiration of bright red blood through the nasogastric tube is ominous, as it signifies fresh brisk arterial bleeding.

Laboratory investigations in an acute bleed do not necessarily help, as the hematocrit and the hemoglobin may not show a significant change for over 12–24 hours.

Identification of High-Risk Patients

It is important to identify high-risk patients as soon as possible. Management in these patients should be as per a planned protocol if morbidity and mortality are to be reduced. The following factors are indicators of poor prognosis in upper GI bleeds—

- Increased age—patients over 60 years of age are at greater risk, particularly in severe bleeds or recurrent bleeds.
- The presence of shock (in particular, a systolic BP <90 mm Hg) and the necessity for multiple transfusions.
- Variceal bleeding in a cirrhotic patient—the poorer the liver function, the worse the prognosis (see Chapter Critical Care in Acute Hepatic Failure).
- The presence of a continuing bright red nasogastric aspirate, or the passage of fresh blood via the rectum.
- Bleeding from a large (>2.5 cm) gastric or duodenal ulcer.
- Hematocrit less than 30%.
- Recurrent bleeding during the same admission.
- The presence of a coagulopathy.
- The need for emergency surgery.

The factors indicating poor prognosis are listed in Box 2.

Determining the Cause of the Bleed

Hematemesis always indicates an upper GI bleed. So does the presence of fresh or altered blood in the nasogastric aspirate

Box 2: Factors indicating poor prognosis in upper gastrointestinal bleeding

- Increased age (>60)
- Presence of shock (systolic BP <90 mm Hg) and necessity for multiple transfusions
- Severe variceal bleeding in a cirrhotic patient
- Recurrent bleeding in presence of bright red nasogastric aspirate, or passage of fresh blood via rectum
- Bleeding from a large (2.5 cm) gastric or duodenal ulcer
- Hematocrit <30%
- Recurrent bleeding during the same admission
- Presence of a coagulopathy
- Need for emergency surgery

in a patient who only has maelena. Maelena in the absence of hematemesis or blood in the nasogastric aspirate suggests a bleed from a lesion in the small bowel, cecum or ascending colon. Though fresh blood is most often seen in a bleed from the large bowel or a fresh bleed from the lower ileum, it can also occur with a massive upper GI bleed. In the latter instance, hemodynamic instability is always present. The presence of hyperactive bowel sounds and a disproportionate rise in blood urea suggests an upper GI lesion. In any case, an upper GI endoscopy should prove or disprove the presence of a lesion in the esophagus, stomach or duodenum responsible for a bleed.

History and physical examination may occasionally suggest the specific disease. In a patient, who is in shock, the history should be brief and quick because of the need for emergency resuscitation. A complete history should be obtained after the patient has been stabilized. History should include the prior use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), or the use of anticoagulants or antiplatelet drugs. A history suggestive of peptic ulcer disease prior to the present episode of bleeding may point to a correct diagnosis. A history of violent retching and vomiting prior to hematemesis suggests a Mallory-Weiss syndrome. A history of chronic alcoholism may suggest liver cirrhosis. The medical history should include past episodes of GI bleeding and their causes (if ascertained).

Clinical examination should be thorough and not just confined to the examination of the abdomen. The abdomen should be carefully palpated for tenderness, guarding, rigidity, palpable masses and percussed for the absence or presence of free fluid; auscultation of bowel sounds should never be omitted. It is important to determine the circulatory state and to look out for background comorbid disease involving other major organ systems of the body. Relevant blood and other investigations should be promptly sent for. These have been listed in the section on Management.

Management

Major upper GI bleeds are best managed jointly by an intensivist, physicians (the team should include a GI specialist), an endoscopist and a surgical team. Obviously such bleeds require intensive care. Indications for transfer to critical care in a patient admitted to the wards for a GI bleed have been mentioned earlier.

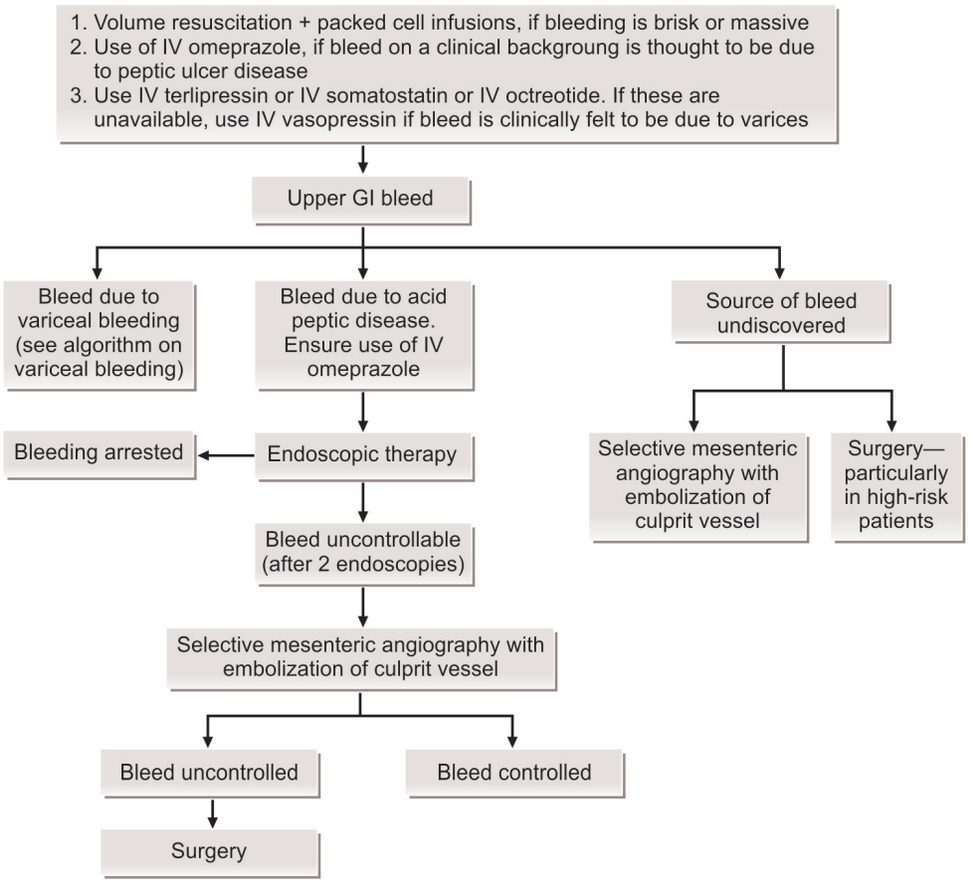
On admission, blood is withdrawn for grouping and cross-matching, as also for routine baseline hematological and biochemical parameters. A large bore catheter is inserted into a peripheral vein, and volume replacement by infusion of crystalloids (and if need be, also by colloids) started (see Chapter Hypovolemic and Hemorrhagic Shock). Investigations should include a blood count, hematocrit, platelet count, and a basic coagulation profile—clotting time, prothrombin time, partial thromboplastin time. It should always include full liver function tests including serum proteins and serum albumin concentration; serum electrolytes, blood urea, and creatinine should also be estimated. Arterial blood gas analysis is done as a baseline study and an electrocardiogram (ECG) tracing obtained. A serum amylase should always be done, as, in rare instances, acute pancreatitis may present with a severe upper GI bleed. An X-ray of the abdomen in the standing posture (if this is possible) is a routine investigation. Continuous ECG monitoring is advised, particularly in older patients, in those with a history of cardiac disease, and in those whose ECG tracing is abnormal. A Foley's catheter is inserted in patients with severe bleeds so that an hourly urine output chart is maintained. Intake/output charts are mandatory.

A central venous line is also promptly secured and connected to a pressure monitor. It is generally not necessary to monitor the left ventricular filling pressures except in those receiving massive transfusions and in older patients with known severe left ventricular disease or dysfunction. In the above high-risk group of patients, a Swan-Ganz catheter is inserted so that infusions of fluids and blood are carefully monitored to prevent pulmonary edema.

A nasogastric tube should be passed expeditiously, immediately after a peripheral vein has been secured and volume replacement started. The stomach is aspirated; the contents with regard to their nature and quantity are noted. A half hourly or one hourly chart of aspirated contents is maintained. Gastric lavage is performed through the wide bore nasogastric tube. We prefer to use iced saline to which adrenaline or noradrenaline has been added. Cold tap water probably does just as well; in fact, the current trend is to use cold tap water for lavage instead of ice cold saline. Frequent aspiration following lavage is important not only to note the degree of continuing bleed, but also to prevent aspiration into the lungs, and to allow a good view for endoscopy. At times, blood gets clotted within the stomach, and cannot be aspirated even through a very wide bore tube. Intravenous metoclopramide or IV erythromycin can help to induce gastric emptying and clear the stomach of clots and blood, so as to allow a better and more effective endoscopic view.

Meanwhile, volume replacement should be rapid and its effects should be apparent by a stable blood pressure, improved urine output and improved tissue perfusion. To replace the loss of Hb, or in a massive bleed, urgent blood

Flowchart 1: Flowchart showing management of an upper gastrointestinal bleed


1. Volume resuscitation + packed cell infusions, if bleeding is brisk or massive
2. Use of IV omeprazole, if bleed on a clinical backgroung is thought to be due to peptic ulcer disease
3. Use IV terlipressin or IV somatostatin or IV octreotide. If these are unavailable, use IV vasopressin if bleed is clinically felt to be due to varices
Upper GI bleed
Bleed due to variceal bleeding (see algorithm on variceal bleeding)
Bleed due to acid peptic disease. Ensure use of IV omeprazole
Source of bleed undiscovered
Bleeding arrested
Endoscopic therapy
Selective mesenteric angiography with embolization of culprit vessel
Surgery—particularly in high-risk patients
Bleed uncontrollable (after 2 endoscopies)
Selective mesenteric angiography with embolization of culprit vessel
Bleed uncontrolled
Bleed controlled
Surgery

transfusions are indicated. In cases where there is no time for grouping and cross-matching, O Rh-negative blood is transfused. It is preferable to give packed-cell infusions instead of whole blood whenever these are available. Over-transfusions carry the immediate risk of pulmonary edema. One unit of fresh frozen plasma should be preferably administered for every 3 units of packed red cells. The details of volume replacement have been dealt with in the Chapter Hypovolemic and Hemorrhagic Shock.

Patients with cirrhosis of the liver and patients on warfarin will have a raised INR and will need adequate infusions of fresh frozen plasma to correct these coagulopathies. Patients receiving aspirin or clopidogrel may require platelet infusions to counter platelet dysfunction. GI bleeds occurring in renal failure and uremia may respond to the administration of IV desmopressin (0.3 µg/kg), a vasopressin analogue that promotes von Willebrand factor release from endothelial cells.[7,8]

Once adequate restitution of volume and blood has been instituted and the patient is hemodynamically stable, an upper GI endoscopy should be performed. Esophagogastroduodenoscopy provides a diagnosis in more than 90% of patients scoped within 24 hours of a bleed. If this procedure is delayed for more than 48 hours, the diagnostic sensitivity drops to 33%. Endoscopy not only is essential in providing a diagnosis as the cause of the bleed, but it also provides therapeutic options. In fact, diagnostic and therapeutic procedures can be achieved at the same time. Endoscopy is not completely without risk. The complication rate is about 0.9% with an incidence of one death in 700 examinations in the acutely bleeding patient.[9] When aspiration of stomach contents is a major risk, the procedure should be done under anesthesia, after electively intubating the patient with an endotracheal tube. Continuous ECG monitoring and monitoring of oxygen saturation is imperative during the procedure.

In patients who have been bleeding and continue to bleed actively on admission, endoscopy may not be able to offer a diagnosis because of presence of large clots and fresh blood within the stomach cavity. In these patients, a selective mesenteric angiography helps to determine the vessel that is bleeding. Once an arterial source of bleeding is clearly identified on selective mesenteric angiography, the culprit vessel is embolized. The success rate (to stop bleeding) is close to 90%. Ischemic complications are rare in the upper GI tract because of the presence of many collaterals in contrast to the comparative poverty of collaterals in the lower GI tract.

The prognosis is indeed grim if selective mesenteric angiography fails to identify the bleeding vessel and the patient continues to bleed. Surgery is then the only option, but unquestionably carries a very high mortality. The therapeutic procedures (which often go hand in hand with diagnostic procedures) are discussed at greater length in the section of the Management of Specific Disorders.

Important Specific Causes of Upper Gastrointestinal Bleed

Peptic Ulcer Disease

Peptic ulcer disease is the commonest cause of an upper GI bleed. Acid peptic disease, besides gastric and duodenal ulcers, also includes gastric and duodenal erosions, stress ulcers and reflux esophagitis. The use of NSAIDs and *H. pylori* infections are important etiological factors. Severe PUD bleeding is most often due to an ulcer on the posterior wall of the duodenum eroding the gastroduodenal artery. The bleeding may stop spontaneously in the majority of patients but about 20% or more may continue to bleed. This is one condition where early use of a proton pump inhibitor (PPI) suitably increases intragastric pH and helps to arrest bleeding so that endoscopic therapeutic procedures may not be necessary.[10] PPI have been shown to be more effective than H_2 receptor antagonists or somatostatins.[11,12]

Once the diagnosis of a bleed due to PUD has been made on endoscopy, omeprazole is administered as an 80 mg IV bolus, followed by an 8 mg/hour continuous infusion for 72 hours followed by 40 mg twice daily, morning and evening for 2 weeks. These large doses of PPI have been shown to decrease the incidence of recurrent bleeding,[12-15] decrease the need for surgery and prevent the development of shock with an associated increase in morbidity and mortality. Prompt endoscopy is essential and as mentioned in the previous section, should be performed early (Flowchart 1).

Endoscopic Measures to Arrest Bleeding in Peptic Ulcer Disease

Local measures through the endoscope to stop bleeding include local injection of epinephrine, thermocoagulation and use of a bipolar probe, argon laser coagulation and application of endoscopic clips. When used alone or in combination, these methods successfully control bleeding in 90% of cases.[16] Epinephrine is injected locally in a dilution of 1:10,000; it arrests bleeding through direct vasoconstriction, through tamponade of the bleeding site if a large enough volume has been injected and through inducing increased platelet aggregation.[17,18] Rebleeding can, however, occur in 20% of patients.[13] A Cochrane database review suggested that the addition of an alternative modality to epinephrine injection, reduced further bleeding from 18.5% to 10.4%, the need for emergency surgery from 10.8% to 7.5% and mortality from 5% to 2.5% in high-risk ulcers.

Thermal coagulation is more effective in preventing rebleeding and the need for surgery but is associated with a very small risk (1%) of perforation.[19] Hemoclips are also very effective when applied endoscopically but require special expertise.

Even after endoscopic procedures have been successful in arresting bleeding, bleeding recurs in about 20% of patients with a significant increase in morbidity and mortality.

Elmunzer et al.[16] reported on the following predictive factors for rebleeding—hemodynamic instability, large ulcer (>2 cm), a posterior duodenal or lesser curvature ulcer and multiple comorbidities. The Forrest Classification has also been found to be useful in predicting rebleeding.[20] Forrest I lesions are those that are actively bleeding. Forrest II has stigmata of recent bleeding. Forrest IIa lesions are those where a nonbleeding ulcer is visible; Forrest III are lesions showing the presence of an adherent clot. Forrest III lesions show no signs of active bleeding. Forrest I and II have a high incidence of rebleeding and nearly all have a rebleeding rate of between 40% and 50% and are associated with a mortality of 11%. Endoscopic treatment is recommended for all Forrest I and IIa lesions. The treatment of Forrest III lesions is not well-defined. Most endoscopists are hesitant to remove an adherent clot for fear of rebleeding. Administration of PPIs helps to stabilize the clot and perhaps reduces the chance of rebleeding (Table 1).

Table 1: Risk factors for continued bleeding or rebleeding from peptic ulcer

Endoscopic finding	*Proportion that continues to bleed or rebleed (%)*
Arterial bleeding	90
Nonbleeding visible vessel	40–45
Adherence clot	10–25
Oozing	<20
Flat pigment spot	<10
Clean ulcer base	<5

Sources: Data from NIH Consensus conference: Therapeutic endoscopy and bleeding ulcers. JAMA. 1989;262(10):1369-72.
Swain CP. Pathology of bleeding lesions. In: Sugawa C, Schuman B, Lucas C (Eds). Gastrointestinal Bleeding. New York, Igakushoin; 1992. p. 26.
Laine L. Rolling review: upper gastrointestinal bleeding. Aliment Pharmacol Ther. 1993;7(2):207-32.

Angiography

If bleeding fails to stop and continues to recur in spite of one or more endoscopic attempts, angiography is advised. Angiography is also promptly advised if endoscopy fails to diagnose the site of bleed or if the stomach is so filled with blood and clots that visibility through the endoscope is very poor. If a bleeding site cannot be identified through angiography, blind embolization should not be done. However, if endoscopy had identified the site of bleed, embolization of suspected vessels/vessel is often as effective as targeted embolization.[21-23] If rebleeding takes place after the first embolization, a second

embolization may be effective, the combined success rate being 95%.[21] An important complication of an angiographic procedure is acute renal failure, particularly if excessive amount of dye has been used, or in patients with a background of renal disease. Volume depletion caused by severe bleeds accentuates the nephrotoxic effect of the dye. Ischemia to the upper GI tract is rare after angiographic embolization because of the plentitude of collateral vessels in this area of the gut. Duodenal ischemia may, however, occur and should be treated conservatively with PPI.

Surgery

A small minority of patients require surgical intervention to control bleeding. It is indicated if endoscopic and/or angiographic embolization has failed to control the bleed. These patients are usually quite ill and have a higher mortality, the mortality rate after failed embolization being as high as 80%. The older the patient, the sooner must a surgery be decided upon if endoscopic and angiographic measures have failed. Recurrence of a bleed at the same admission uncontrolled by endoscopy is also an indication for surgery. The need for more than 8 units of blood in 24 hours in the presence of active bleeding is again an indication for surgery. Finally, massive bleeds with the patient remaining well-nigh pulseless with severe hypotension is in our unit an indication for emergency surgery as there is no time for any nonsurgical therapeutic procedures. Well-nigh moribund patients have come alive if the surgeon in a matter of minutes has identified and clamped the spurting artery at the base of a large peptic ulcer.

The surgical procedure of choice is oversewing of the bleeding vessels, if possible, combined with a vagotomy and pyloroplasty, vagotomy and antrectomy, or a highly selective vagotomy. Extensive surgery is not warranted because of the very effective acid-suppressive drugs available. In units where angiographic facilities for selective embolization are unavailable (and there are many such units in India and poor developing countries), surgery is indicated when (1) endoscopic attempts have failed to arrest bleeding; (2) when transfusion requirements are more than 8 units over 24 hours; (3) in patients with rebleeds and (4) in massive bleeds when there is no time for non-surgical modalities. The older the patient, the more important it is not to delay surgery under the above circumstances.

Bleeding Esophageal Varices

The management of this dangerous complication of cirrhosis of the liver has been dealt with in another chapter (Critical Care in Acute Hepatic Failure). Patients with portal hypertension may also bleed from a diffuse abnormality of the gastric mucosa, a condition called portal hypertensive gastropathy. Medical measures to counter acute bleeds are the same as in variceal bleeding. Prevention of future rebleeds may perhaps be helped by the use of propranolol 20 mg thrice daily and sorbitrate 5–10 mg thrice daily.

Stress Ulcers[24-26]

Single or multiple superficial gastric, duodenal or gastroduodenal ulcers often occur in critically ill patients. They can on occasions bleed profusely, and carry a significant mortality. It is important to prevent these ulcers from bleeding and, if possible, from forming. Patients at risk from these lesions include those with burns, head injury, multiple trauma, acute liver cell failure, acute renal failure, Gram-negative sepsis and disseminated intravascular coagulopathy. Patients on prolonged mechanical ventilation and those suffering from acute or fulminant illnesses (tetanus, *Plasmodium falciparum* infections) are also prone to acute mucosal erosions. Cook et al.[27] noted that bleeding from stress ulcers occurred only in patients who required mechanical ventilation or had coagulopathy. This is not our experience; bleeding from gastroduodenal erosions can occur in any critically ill patient with major organ system dysfunction.

Prophylaxis from stress ulcers is generally provided by the use of sucralfate as this counters acidity without unduly raising the pH of gastric contents. In high-risk cases, prophylaxis with PPIs or H_2 receptor antagonists is acceptable. If stress ulcers cause bleeding, IV PPIs should be used in large doses as mentioned under the specific management of PUD. PPIs increase intragastric pH more effectively than H_2 receptor antagonists and are believed to be more effective for prevention of gastroduodenal erosions caused by aspirin.[28]

In our unit, bleeding acute erosive gastroduodenitis from any cause is also treated by a continuous infusion of cold milk containing magnesium hydroxide and norepinephrine, given through the nasogastric tube. This generally stops bleeding. In critically ill patients in whom oral feeds are contraindicated, endoscopic methods to stop bleeding may prove effective. Failing this, angiographic therapy, either in the form of a vasopressin infusion into the left gastric artery, or embolization of the left gastric artery should be tried. *Every effort should be made to avoid surgery in these patients, as surgery carries a forbidding mortality.*

Mallory-Weiss Tear

Mallory-Weiss tear is most often observed along the esophagogastric junction. It is most common in young males who often give a history of severe vomiting or retching, coughing or straining, prior to the hematemesis. Mallory-Weiss tears are commonly associated with alcohol abuse, hiatus hernia and possibly with *H. pylori* infection. A correct diagnosis is easily made at endoscopy. Most tears stop bleeding spontaneously. Some may, however continue to bleed massively. If bleeding continues, band ligation or hemoclips usually arrest it.[29,30] Local injections of epinephrine also help. Thermocoagulation has also been tried but its use requires further evaluation. If these methods fail, arteriographic embolization or surgery may be necessary.

Aortoenteric Fistula

These invariably occur in patients who have an aortic graft in situ. The diagnosis should be suspected whenever a patient with an aortic prosthesis suffers an upper GI bleed.

The communication with the aorta can occur along any portion of the gut but is generally with the third part of the duodenum, so that the patient has both hematemesis and maelena, with all the hemodynamic effects of a severe bleed. Aortoenteric fistula usually occurs following graft-related sepsis. Endoscopy should be performed to exclude more proximal lesions. A CT scan shows gas in the retroperitoneal space. Aortography may fail at times to reveal the fistula. Treatment is surgical and should be performed as soon as the hemodynamic state has been improved by immediate rapid volume replacement. Endovascular repair has been reported,[31-33] but should be used as a temporary measure before definitive surgical repair. Endovascular repair remains an option in patients with a short life expectancy, as in those suffering from advanced cancer.

Dieulafoy's Lesion

A Dieulafoy's lesion is a large anomalous artery responsible for 2% of upper GI bleeds.[34] This lesion can occur anywhere along the digestive tract but is most frequently present in the fundus along the lesser curvature of the stomach. This bleeding site can be easily missed by even an experienced endoscopist, more so as it bleeds intermittently. Its appearance is that of 1–3 mm bleeding arteriole protruding through the mucous membrane. It is dealt with endoscopically by epinephrine injection, by electrocoagulation or heat coagulation, and/or clips. Occasionally, angiographic embolization is needed to stop the bleed. Mortality is close to 20%, particularly in older individuals, chiefly because of associated comorbidities.[34]

Even a moderate-sized bleed complicating a critical illness can markedly enhance its gravity, and ultimately be responsible for the patient's death. Finally, patients with upper GI bleeds who have large clots in their stomach are at a considerable risk for sepsis. Most of these patients have received large doses of antacids, and the additional presence of blood clots form an excellent medium for the overgrowth of dangerous Gram-negative organisms. We have seen Gram-negative sepsis kill these patients, even after definitive surgery has been successfully performed.

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UPPER GI BLEEDS IN THE IMMUNOCOMPROMISED

Upper GI bleeds in the immunocompromised may be due to all the conditions listed above. In addition, immunocompromised patients may suffer a GI bleed because of infection by opportunistic organisms. Opportunistic infections involving the esophagus, stomach, duodenum and at times other parts of the GI tract include the cytomegalovirus, herpes simplex virus, fungal infections, notably candida, and rarely aspergillus and mucor. These infections can cause inflammation of the mucosa, erosions, ulcerations. They can be diagnosed through endoscopy, biopsy, with appropriate staining and histopathological study of the biopsy material. The prognosis is often grim in spite of appropriate specific treatment, death being due to uncontrollable bleeding or perforation.

BLEEDING FROM THE SMALL BOWEL

Till recently, bleeding from the small bowel was considered under the category of lower GI bleeding. It is best considered as a separate entity because of the newer diagnostic procedures and therapeutic applications used both for diagnosis and control of these bleeds.

Prakash and Zuckerman[35] in their cohort of 29 patients with small intestinal bleeds reported that bleeding from the small bowel had worse outcomes compared to bleeding from the large bowel.

The two most important causes of small bowel bleeds noted in our unit over several years are angiodysplasias which are noted in elderly patients as also in renal failure, and neoplasms of the small bowel. Neoplasms chiefly include adenocarcinoma of the bowel; rarer tumors like GIST tumors may also to bleed severely. Other lesions include ulcerations caused by aspirin and NSAIDs, inflammatory pathologies as in tuberculous ulcers, typhoid ulcers and Crohn's disease. A solitary jejunal ulcer, the etiology of which is uncertain, is a rare pathology that can cause a bleed and be difficult to detect. Small intestinal varices due to cirrhosis and portal hypertension can also cause brisk blood loss. Meckel's diverticulum is another source of small intestinal bleed, as is the presence of a Dieulafoy's lesion. Non-Hodgkin's lymphoma involving the small gut can also result in bleeding. Ischemia of the bowel, particularly superior mesenteric artery thrombosis (SMAT) or mesenteric vein thrombosis can result in the passage of fresh blood through the rectum. Patients on anticoagulants as also patients who develop coagulopathy can bleed from any site within the body including the small bowel. Investigations are the same as with bleeding from the upper GI tract. These have been listed earlier. As with upper GI bleeds, the first priority is the restoration of volume with crystalloids and colloids and transfusion of packed blood cells in all patients who are hemodynamically unstable because of severe blood loss.

Determining the Cause and Site of the Bleed

This indeed can be difficult. History is often not of much help. A past history suggestive of inflammatory bowel disease is important. Evidence of diffuse atherosclerotic disease in association with episodic abdominal pain may suggest ischemia to the bowel. Painless bleeding is seen with angiodysplasia, Meckel's diverticulum and arteriovenous anomalies. A history suggestive of small bowel obstruction should raise suspicion of a mitotic lesion.

Physical examination should, as with any bleed, determine the hemodynamic and circulatory state. Careful examination of

the abdomen for tenderness, palpable lumps, and for evidence of localized or general peritonitis is important. Examination of other organ systems to determine comorbidities should always be done.

Routine blood investigations are the same as with patients admitted for an upper GI bleed, establishing that the site of bleed in the small bowel is generally by a process of exclusion, e.g. excluding an upper GI bleed and a lower GI bleed.

1. An upper GI scopy is normal—it shows no pathology and the aspirated contents contain acid and bile. This should rule out a bleed proximal to the ligament of Treitz. We have, however, seen one patient where a bleed from the proximal jejunum regurgitated backward through the duodenum, leading to both hematemesis and maelena.
2. A colonoscopy is again normal—this can only be ascertained if a clear view is obtained and the colon is not filled with fresh or altered blood.
3. If both upper and lower scopies show no definite pathology, the bleeding is presumed to be from the small bowel. The following diagnostic tests are now set into motion. Diagnostic tests and therapeutic interventions often go hand in hand.

The protocol followed is detailed below—

- A standing plain X-ray of the abdomen followed by high resolution computed tomography of the abdomen with IV contrast + oral contrast are performed. Edema localized to a portion of the small gut, ulceration of the mucosa, strictures, or the typical cobblestoned mucosa of Crohn's can be picked up easily. An intraluminal mass within the small gut can also be evident. Edema of the wall of a localized segment of the gut with prominence of the mucosal folds is an early imaging sign of mesenteric artery thrombosis, which can be substantiated by mesenteric angiography.
- Enteroclysis (small bowel enema), a procedure in which contrast is instilled directly into the duodenum together with methyl cellulose and air allows better visualization of the lumen, mucosa and the wall of the small gut.
- Mesenteric angiography which can be highly selective reaching out to small vessels supplied by the superior mesenteric artery is in our opinion best suited to quickly identify the exact site of bleed. If found this can be promptly embolized.

Mesenteric angiography may fail if the bleed is intermittent and the procedure is performed at the time when the bleed has temporarily stopped or is negligible.

In the presence of a severe bleed with hemodynamic instability a mesenteric angiography should be the first diagnostic (cum therapeutic) procedure performed.

If a mesenteric angiography is noncontributory, the following tests can be done—

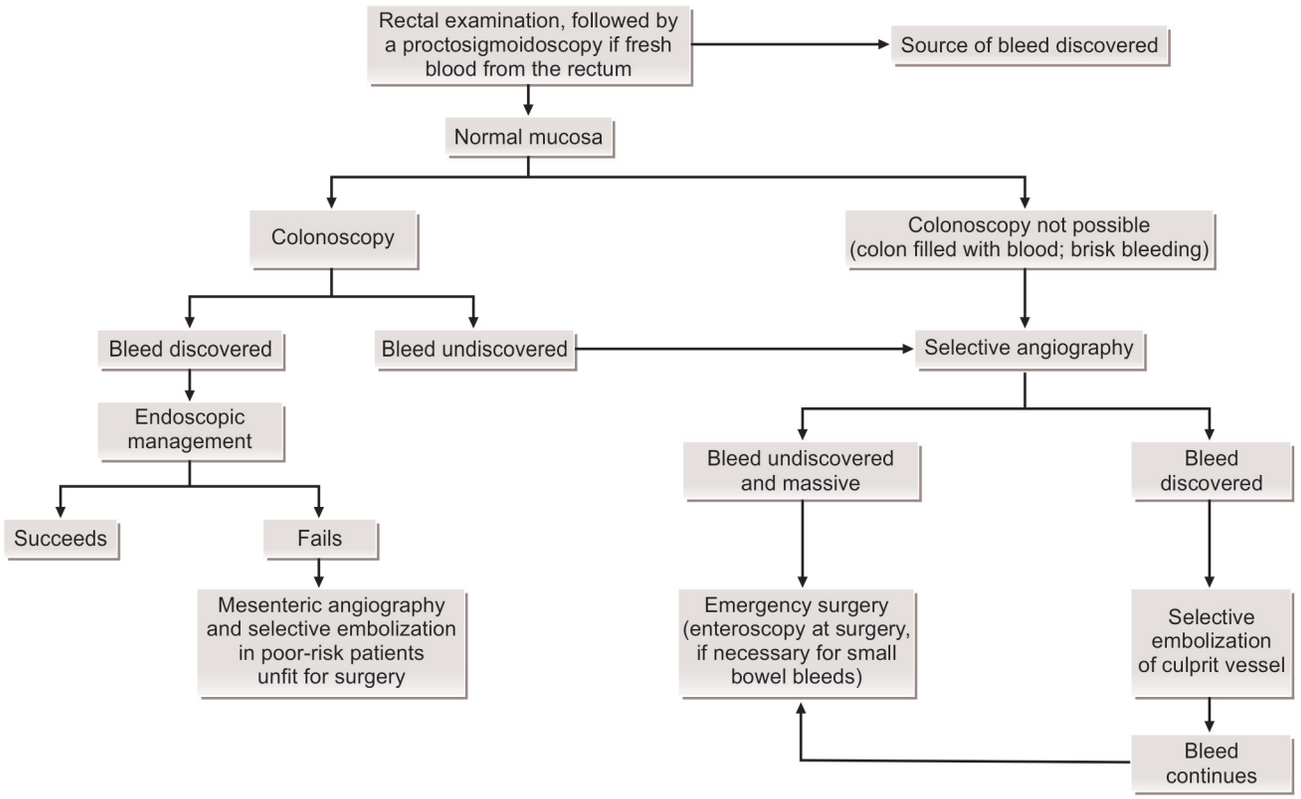
- ^{99}Tc tagged red blood cell (RBC) scan is commonly used to define the site of bleed; it, however, gives both false positive and negative results and we have rarely found this test to be useful in detecting significant small bowel bleeds.
- Push enteroscopy with a dedicated video enteroscope allows the visualization of the proximal 50–100 cm of the small bowel. This procedure can be both diagnostic and therapeutic.
- Double-balloon enteroscopy is a relatively new technique that allows complete visualization of the small bowel.[36-38] It uses a 200-cm enteroscope with two balloons, one attached to the tip of an endoscope and the other to the tip of a flexible overtube. The balloons are sequentially inflated, allowing the advance of the endoscope without looping. The enteroscope can be inserted orally or through the anus, or both, to examine the entire small bowel. This enteroscope can localize the site of bleeding, can take biopsies and also allow therapeutic interventions (adrenaline injections, thermocoagulation) to stop bleeds.
- Wireless capsule endoscopy. Capsule endoscopy is a comparatively new technique. The procedure has three components—(1) a capsule endoscope; (2) an external receiving antenna with an attached portable hard drive, and (3) a personal computer workstation for review and interpretation of images. The capsule is swallowed on a fasting stomach and the images are reviewed as the capsule finds its way down the GI tract. Adverse effects include failure of the capsule to progress through the bowel. GI obstruction or pseudo-obstruction is a contraindication to capsule endoscopy. Capsule endoscopy is reported to have a success rate of 67%[39,40] to as high as 92%.[41] The procedure does not yield reliable results during a massive bleed when the bowel is choked with blood. Unfortunately, this is just the situation where determining the site of bleed is of crucial importance. We have not found the use of capsule endoscopy helpful in situations which are urgent and where it really matters.

Our critical care and GI unit have no experience with enteroscopes. Therefore, when confronted with a severe life-threatening GI bleed not identified by an upper GI scopy or a colonoscopy, we promptly opt without further delay for a mesenteric or celiac artery angiography. If the bleeding site is determined, it is embolized. If there is rebleeding after a lapse of time, the site is embolized for the second time. If a situation arises where mesenteric angiography has failed to identify the site of bleed, we promptly opt for an emergency laparotomy. An intraoperative enteroscopy (performed through a colonoscope) is the best means for evaluating the small bowel. As yet, we have always managed to identify the site of bleed in all difficult problems by this method. Once identified, the site of bleed can be dealt with appropriately.

LOWER GASTROINTESTINAL BLEEDING

Patients with lower GI bleeding present with hematochezia or blood per rectum. It is important to note that very brisk bleeding from the upper GI tract may also present with hematochezia; these patients (as mentioned earlier), however, are always hemodynamically unstable and are invariably hypotensive.

Flowchart 2: Algorithm for bleed from small bowel or large bowel—patient presenting with fresh blood per rectum or maelena. Upper gastrointestinal excluded by an upper GI scopy


Rectal examination, followed by a proctosigmoidoscopy if fresh blood from the rectum
Source of bleed discovered
Normal mucosa
Colonoscopy
Colonoscopy not possible (colon filled with blood; brisk bleeding)
Bleed discovered
Bleed undiscovered
Selective angiography
Endoscopic management
Bleed undiscovered and massive
Bleed discovered
Succeeds
Fails
Mesenteric angiography and selective embolization in poor-risk patients unfit for surgery
Emergency surgery (enteroscopy at surgery, if necessary for small bowel bleeds)
Selective embolization of culprit vessel
Bleed continues

Note: If after colonoscopy or mesenteric arteriography, the bleed is undiscovered, a push enteroscopy or wireless capsule enteroscopy may be tried to determine the source of the bleed, provided the bleed is not massive and life-threatening and the necessary expertise is available. Push enteroscopy can be combined with therapeutic endoscopy.

Occasionally, bleeding from the right colon may present as maelena because of a longer transit time. Common, important causes of bleeding from the lower GI tract include colonic diverticulosis, angiodysplasia, inflammatory bowel disease, amebic ulcerations of the large bowel and neoplasms.

Investigations are as with bleeding from any site, and have been detailed in the section on upper GI bleeding. The importance of quick restoration of body fluids and transfusions of packed RBCs in severe bleeds must commence immediately to restore hemodynamic stability.

As with GI bleeds described earlier in this chapter, the first diagnostic modality for determining the site of the bleed is through endoscopy—colonoscopy for lower GI bleeds. If this is unrewarding, a mesenteric angiography is done. Diagnostic and therapeutic procedures run hand in hand as with the management of upper GI bleeds and bleeds arising from the small bowel (Flowchart 2). Specific diseases causing lower GI bleed will now be discussed.

Colonic Diverticulosis

Diverticulosis is common, so that bleeding from diverticular disease should be diagnosed only if active bleeding is observed to originate from diverticuli at colonoscopy. Bleeding from diverticuli in the right colon is also fairly frequent. Hence the futility of doing a left hemicolectomy in the hope of stopping bleeding in a patient with diverticular disease when the exact site of diverticular bleeding has not been identified. Bleeding in some of these patients can be massive so that colonoscopy is non-informative. Arteriography may demonstrate the bleed in these instances. The reported success rate with superselective embolization exceeds 85% and the incidence of clinically significant colonic ischemia is low (<5%).[42] If colonoscopy can identify the site of bleeding, control over the bleeding site can, at times, be achieved by the local injection of epinephrine or vasopressin. However, selective embolization offers better long-lasting results and is of obvious advantage in poor risk patients. If bleeding from the colon persists, and the patient is stable and is a good surgical risk, surgical resection of the bleeding site is often recommended. It is, however, critical to identify the bleeding site before surgery. In a retrospective review, blind resection of a "suspected" segment of the colon carries a high mortality. If colonic bleeding is profuse and the site through diagnostic procedures cannot be identified, a subtotal rather than a segmental colectomy is recommended.[43]

Angiodysplasia[37-39]

Arteriovenous malformations become increasingly common with age. The lesions are focal, submucosal and most often present in the cecum. Multiple lesions occur in less than 25%

of patients. Lesions are also often found in the ascending colon and may occur in other parts of the gut, including the small bowel. Angiodysplasia can cause a steady constant ooze of blood, which over a period of time in an elderly patient may prove life-threatening. The lesions are frequently visualized through a colonoscope and can be treated endoscopically by injecting adrenaline, by heat, or by electrocoagulation of bleeding points. It is recommended that for actively bleeding angiodysplasias, treatment should start at the periphery of the lesion so as to tackle the feeding vessels and then go to the actively bleeding area. Endoscopic treatment however carries some hazard because of the thinness of the wall of the cecum and ascending colon. As the lesion is focal, it is also amenable to treatment by arterial embolization at angiography. Continuing massive bleeding, unarrested by colonoscopic procedures or by embolization, requires surgery. Since these lesions chiefly involve the right colon, a right hemicolectomy is indicated.

Ischemic Bowel Disease[44]

Ischemic colitis can cause recurrent pain, diarrhea and bleeding per rectum. At times, the clinical picture resembles ulcerative colitis. Old age, diffuse atherosclerotic disease and atrial fibrillation are important background factors in ischemic colitis. Younger patients with diabetes, connective tissues disease, sickle cell disease and pancreatitis are also at risk. Ischemia in older patients is often precipitated by hypotension from any cause. Colonoscopy shows purplish discoloration of segments of the bowel, with focal areas of mucosal ulceration. Barium contrast studies may reveal thumb-printing of the colonic wall. Mesenteric angiography may show arterial or venous occlusion.

Management is conservative. It should ensure that the patient is not volume-depleted. The cardiac state should be improved, and the ventricular rate slowed appropriately if there is an atrial fibrillation. Fulminant disease leads to necrosis of the colonic wall, and will require surgical resection. These patients invariably have serious background disease; multiple organ failure is a common complication. The mortality in severe ischemic colitis necessitating surgery is often close to 50%.

Inflammatory Bowel Disease

The two inflammatory bowel diseases that occasionally cause massive colonic bleeds are ulcerative colitis and Crohn's disease.

Severe life-threatening continuous bleeding may necessitate emergency colectomy. Ten percent of emergency colectomies performed for the management of complications of ulcerative colitis are because of massive colonic bleed.

Massive bleeding (1%) in patients with Crohn's disease also needs emergency surgery.

Medical treatment should undoubtedly be initiated first. Endoscopy can occasionally be both diagnostic and rarely therapeutic. Angiography may also play a role in both diagnosis and therapy. Massive bleed in severe ulcerative pancolitis is, however, generalized and invariably needs subtotal colectomy and ileostomy.[45] If surgery is contemplated in massive bleeding from Crohn's disease, the site of bleed should be identified as most of these bleeds originate from lesions within the small bowel. Limited resections should be done in these patients.

Neoplasia

Massive bleeds from neoplasms as in patients with non-Hodgkin's lymphoma are uncommon. Colonic polyps can occasionally bleed spontaneously or more often after resection. Major bleeding after resection of a polyp is invariably arterial. It can be treated endoscopically with injection of epinephrine or thermocoagulation. If this is ineffective, superselective angiography with embolization of the culprit vessel is invariably successful.

Rectal Bleeding

Severe rectal bleeding is rare but can occur. It accounts for only 2% of lower GI bleeding. Hemorrhoids are the most frequent cause; severe bleeding is noticed in patients with portal hypertension, and in patients receiving anticoagulants, aspirin or clopidogrel.

Bleeding piles may, at times, hide a more proximal lesion in the proximal colon. A colonoscopy should therefore, always be done. At the same time, it should be noted that the rectal bleeding from hemorrhoids may occasionally be so profuse that blood not only leaks out but extends inward and fills the colon. At colonoscopy, a doubt arises whether there is a proximal colonic lesion (because of blood in the colon) even though there is none.

A solitary rectal ulcer is another possible cause of rectal bleeding in elderly persons. These elderly patients are often bedridden, debilitated with many comorbidities. Bleeding can be life-threatening and therapeutic approaches include endoscopic thermocoagulation, placement of vascular clips and transanal sutures.[46] An important cause of profuse rectal bleeding is from radiation-induced proctitis following treatment of prostate cancer. Radiation results in endarteritic occlusion of vessels, which is followed by the formation of multiple telangiectatic vessels that are prone to bleed. Bleeding can occur within months or even some years after radiation.

Finally, in critically ill people who are constipated with hard stools filling the colon, stercoral ulcers can be the source of severe bleeding. Pressure over devitalized colonic mucosa, poor mucosal and submucosal blood supply are the contributing factors. After careful evacuation of the bowel, injection of adrenaline and/or thermocoagulation through a colonoscope generally helps to reduce or arrest bleeding.

ACUTE ISCHEMIC INJURY TO THE SMALL BOWEL

Acute ischemic injury to the small bowel is termed acute mesenteric ischemia (AMI). It is most often due to superior mesenteric artery embolism (SMAE), superior mesenteric

artery thrombosis (SMAT) and nonocclusive mesenteric ischemia (NOMI). The latter is observed in low flow states as in shock from any cause or from prolonged hypotension.

Venous forms of AMI result from superior mesenteric venous thrombosis (SMVT).

The end results of small bowel ischemia vary from mild alteration in bowel function to marked deprivation of blood supply causing transmural necrosis, perforation and gangrene.

Acute Mesenteric Ischemia: General Features

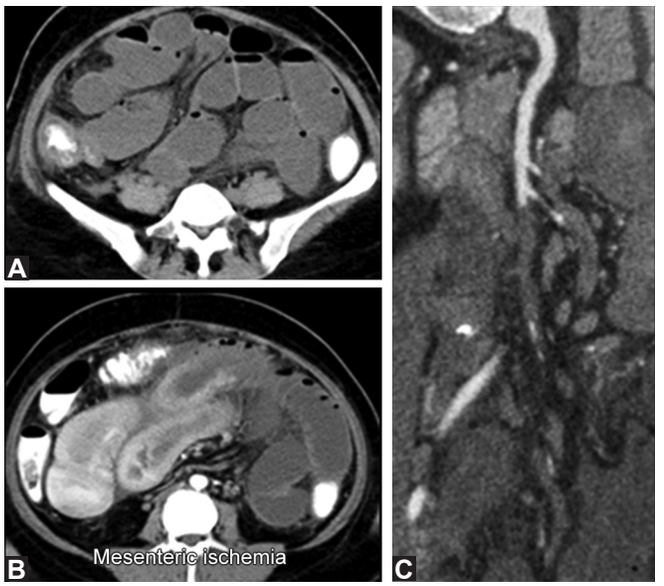
Clinical Presentation

Sudden severe abdominal pain is the first symptom of a block within the superior mesenteric artery. The presence of sudden severe abdominal pain together with a comparatively nonrigid, in fact, normal, feel to the abdomen occurring in a middle-aged or elderly individual should suggest the diagnosis. The diagnosis becomes even more likely if there is associated bleeding per rectum occurring around the time of abdominal pain or soon after it.

If the condition in the early stage is unrecognized, there is now increasing guarding, rigidity of the abdomen and absent bowel sounds. Free fluid may be detected clinically and on ultrasound. These are all features of peritonitis caused by perforation of the necrotic bowel and/or following gangrene of the small bowel following deprivation of its blood supply.

Laboratory Findings and Radiological Study

- Leukocytosis generally over 15,000/cm^3 is invariably present.
- There is a rise in serum lactate levels and around 50% have metabolic acidosis. Rise in serum amylase may offer a wrong diagnosis of pancreatitis. A rise in D-dimer has also been reported.[47]
- Blood culture may be positive as a result of bacterial translocation across the ischemic bowel.
- Plain X-ray of the abdomen is normal (other than ileus) in the standing position. However, an early sign on a high resolution CT scan of the abdomen is thickening of the ischemic bowel wall with significant edema of the mucosal folds. This involves only that segment of the small bowel which is deprived of blood. A contrast CT often shows a clear block in the superior mesenteric artery due to a thrombus. Lack of opacification of the mesenteric vein after injection of contrast is indicative of a clot in the superior mesenteric vein.
- Mesenteric angiography is the mainstay of diagnosis in both occlusive and nonocclusive form of AMI. This allows an early diagnosis, which is important for survival. Angiography has a sensitivity of 75–100% and a specificity of 100%. It also differentiates between occlusive and nonocclusive AMI in most patients. Finally, mesenteric angiography allows treatment by infusion of vasodilator or thrombolytic agents, which can be used at the same time as the diagnostic procedure and which have been shown to improve outcome (Figs 1A to C).



Figs 1A to C: Mesenteric ischemia: (A) CT scan reveals dilated small bowel loops due to ileus; (B) Distal small bowel loops reveal hyperdensity in the wall of small bowel loops as a result of hemorrhage; (C) CT angiography reveals a thrombus in the superior mesenteric artery

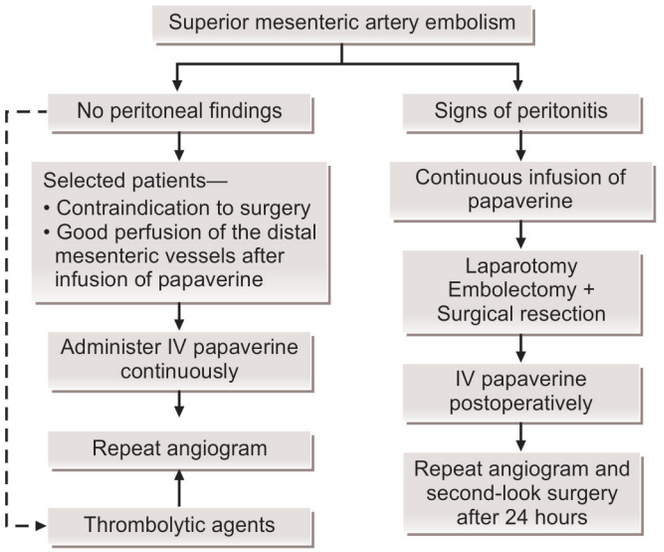
Superior Mesenteric Artery Embolism

Superior mesenteric artery embolism occurs in 50% of patients with AMI. Emboli are generally present at the origin of the superior mesenteric artery or just distal to it. At times, smaller emboli may lodge into distal branches of the superior mesenteric artery.

Treatment

- Volume resuscitation, correction of hypotension, control of congestive heart failure and/or arrhythmias should be promptly achieved.
- In the absence of peritoneal signs, infusion of a vasodilator, such as papaverine administered through the angiography catheter as a continuous drip of 30–60 mg/hour helps to produce vasodilatation of the vasoconstricted, obstructed and non-obstructed branches of the superior mesenteric artery. Relief of mesenteric vasoconstriction is important in the management of AMI from mesenteric emboli. Thrombolytic agents—streptokinase, urokinase, recombinant tissue plasminogen activator have been used with variable success in selected patients.[48,49]
- If signs of peritonitis are present, there is a unanimous agreement that a laparotomy is mandatory with the intent to restore blood flow and resect the necrotic or gangrenous bowel. Blood flow is restored by an embolectomy or arterial bypass. The surgical advice is to resect only the necrotic bowel. If a part of the bowel has questionable viability, it is left alone and a "relook" exploration, also called "second look", is performed 24 hours later. Algorithm for the management of superior mesenteric artery emboli is given in Flowchart 3.

Flowchart 3: Management of superior mesenteric artery embolism



Nonocclusive Mesenteric Ischemia

Nonocclusive mesenteric ischemia is reported to occur in 20–90% of AMIs and result from severe mesenteric vasoconstriction following poor perfusion consequent to shock or hypotension. It is often missed in the intensive care unit and then carries a formidable mortality of 70–90%. It can also occur following large volume shifts as after hemodialysis and in patients with heart failure and arrhythmias. Angiography is the only way to make a diagnosis. Once identified papaverine infusion should be started to relieve vasoconstriction and prevent further ischemia. There is a significant reduction in mortality from 0% to 50% following prompt diagnosis and treatment.[50,51] The infusion is continued and angiography repeated daily until there is no clinical or imaging evidence of persistent vasoconstriction.

Acute Superior Mesenteric Artery Thrombosis

Acute SMAT necessitates immediate surgical intervention with emergency surgical revascularization. Thrombolytic therapy, percutaneous angioplasty and the use of intravascular stents have been attempted. There are often technical problems encountered during the stenting procedure. Restenosis is an important complication.

Acute SMAT generally results from atherosclerotic disease of the superior mesenteric artery, which invariably is just one feature of generalized atherosclerotic vascular disease. Even so, procoagulant factors may be contributory and should always be looked out for, particularly in younger individuals.

Acute Superior Mesenteric Venous Thrombosis

Mesenteric venous thrombosis is comparatively infrequent occurring in 5–10% of patients with acute intestinal ischemia. Symptoms are often nonspecific and diagnosis difficult. Abdominal pain is an important feature occurring in over 90% of patients. It is often not severe and the patient may seek medical attention several days after the onset of pain. Nausea, vomiting and altered bowel habits may be present. CT may demonstrate a central lucency in the superior mesenteric vein, thickening of the bowel wall or dilated collaterals in a thickened mesentery. Angiography demonstrates a thrombosis in the superior mesenteric vein.

If there are signs of peritonitis, an emergency laparotomy is performed with resection of the involved bowel. Mesenteric venous thrombectomy also has a role in the surgical treatment. A "second look" operation needs to be done after 24 hours. Anticoagulation should be carried out routinely following surgery as anticoagulation reduces both recurrence and mortality to a significant extent.

Patients without peritoneal signs are treated with heparin followed by warfarin for a period of 6 months.

It is important to investigate for a procoagulant state in all forms of AMI, particularly in patients with SMAT and in those with SMVT.

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CHAPTER 57

Hemorrhagic Disorders

GENERAL CONSIDERATIONS

Bleeding and hemorrhagic disorders are frequently observed in an intensive care unit (ICU). They are almost invariably acquired and are due to underlying disease, or are iatrogenically induced, most frequently by drugs. Rarely a congenital defect in the bleeding or clotting mechanism is uncovered for the first time in a patient admitted for an acute problem unrelated to this defect. Equally rarely, a patient with a congenital disturbance in his clotting mechanism may be admitted for the critical care of an acute severe bleed. A past history of bleeding and relevant investigations are necessary to determine the exact nature of the congenital defect. This chapter briefly outlines the inherited defects in platelet function and in coagulation that can cause severe bleeding. It also discusses at greater length the acquired disorders of platelets and acquired coagulation disorders, which are far more frequently encountered in critical care units when compared to inherited disorders.

Hemorrhagic disorders in the ICU are due to one or more of the following: (i) thrombocytopenia; (ii) a qualitative defect in the platelets; (iii) damage to capillary endothelial cells and (iv) coagulation defects.

There are some diseases, particularly renal failure, sepsis and multiple organ failure, which cause or are associated with two or more of the above defects. An awareness of the nature of acquired disorders in bleeding and clotting mechanisms, peculiar to important common critical illnesses, is of great importance in management. This is because in poor developing countries, very few centers have facilities for doing detailed coagulation profiles or studies on platelet function. Even when these facilities are available, there is a lag of precious time between the sampling of the blood and the actual results of the analysis. Treatment in severely bleeding patients is therefore empiric. It is however always wise to collect blood for a proper analysis of hemorrhagic disorders, before starting such empiric treatment. Results of such analysis may then help to suitably modify treatment.

CLINICAL APPROACH

History

A good history is all-important, particularly with reference to spontaneous bleeding in the past or to excessive bleeding, following an injury or surgery. Rarely a background suggesting a possible congenital defect in bleeding or clotting, or an acquired one as in immune thrombocytopenic purpura, will be uncovered. Previous coagulation profiles and platelet counts done in the course of an acute illness are also of help in comparing values. A meticulous history regarding intake of drugs is invaluable, as drug-induced disturbances are an extremely important cause of thrombocytopenia in an intensive care setting. Aspirin, non-steroidal anti-inflammatory drugs, the newer synthetic penicillins, ticlopidine, clopidogrel, platelet glycoprotein IIb-IIIa inhibitors, and antihistaminics are amongst the more frequently used drugs responsible for either thrombocytopenia or a qualitative defect in platelet function.

Coagulation defects may be congenital or acquired. Congenital defects, when marked, are generally evident from the history of frequent bleeds since childhood. Acquired coagulation defects are far more frequently encountered in an ICU than congenital defects. As detailed later, acquired coagulation defects occur against a background of severe liver or renal dysfunction, or following consumption of coagulation factors, or in Vitamin K deficiency, or rarely due to circulating

inhibitors of coagulation. A detailed history coupled with a careful physical examination should help uncover most of the background diseases known to produce acquired coagulation defects that result in a bleeding disorder.

Though drugs frequently affect platelets, they very rarely alter coagulation factors qualitatively or quantitatively. There are however several cephalosporins which diminish the production of Vitamin K-dependent coagulation factors. These include cefoperazone, cefamandole and the monolactams. Patients on oral anticoagulants (e.g. warfarin) or on heparin have as expected, an altered coagulation profile. It is worth remembering that, in rare instances, catastrophic bleeding can occur in a patient on warfarin, even when the alteration in the coagulation profile [i.e. the prothrombin time (PT)] is within the therapeutic range. Ten percent of these patients may bleed, and in 1–2% of these cases, the bleeding may be intracranial with catastrophic results.

Physical Examination

Physical examination should have four important objectives—

1. To determine clinically or on relevant tests, the nature of the background disease or critical illness. This suggests the cause and nature of the associated hemorrhagic disorder, which results from the disease.
2. To carefully inspect the site of bleeding or hemorrhage. Petechiae, bleeding from catheters or drains, and bleeding from the gastrointestinal tract, urinary tract and mucous membranes is more commonly observed with thrombocytopenia or a qualitative defect in platelet function. Defects in coagulation factors can also cause bleeding from these sites, but are also associated with deep soft tissue bleeds, retroperitoneal hemorrhage, hemarthrosis or bleeds into internal organs.
3. When bleeding occurs from one local site, e.g. the GI or the urinary tract, it is important to clearly exclude an anatomic cause for the bleed, even in patients with thrombocytopenia or a clotting defect. Not uncommonly, a local pathology and a hemostatic disorder may both be contributory to such a bleed.
4. Inherited disorders of platelets or of coagulation are comparatively rare in the ICU. A good family history, absence of background disease known to cause platelet and coagulation abnormalities, and detailed laboratory hematological investigations generally provide an accurate diagnosis.

Laboratory Tests

Basic screening tests to determine the cause of bleeding include a routine blood count, a platelet count, PT and activated partial thromboplastin time (aPTT). A template bleeding time (BT) was in the past generally included as a screening test to assess qualitative platelet dysfunction. It is now not performed as it was an inadequate predictor of bleeding and platelet function. Now, platelet function is assessed by automated tests, the one most frequently used being the platelet function analyzer. This automated test assesses platelet function with greater sensitivity and reproducibility. Currently, it is felt that even this test lacks enough sensitivity and specificity to test platelet function in qualitative platelet disorders.[1]

Table 1: Interpretation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) in bleeding disorders

PT	*aPTT*	*Interpretation*
Prolonged	Normal	Liver disease Factor VII deficiency/defect Vitamin K deficiency
Normal	Prolonged	Hemophilia A, B, C Lupus anticoagulant Antiphospholipid antibody
Prolonged	Prolonged	Advanced liver disease, vitamin K deficiency, warfarin therapy, disseminated intravascular coagulation, fibrinogen deficiency/defect, factor II, V or X deficiency or defect
Normal	Normal	Thrombocytopenia, platelet dysfunction, α_2 antiplasmin deficiency, factor XIII deficiency

There is much that can be inferred from a *CBC*, *platelet count*, *PT*, and *aPTT*, as is evident from Table 1.

Further Tests to Assess Bleeding[2]

Thrombin Test

Many units do this test routinely for assessing a bleeding disorder. The thrombin test measures the conversion of fibrinogen into fibrin. This test is prolonged if the patient is on heparin or there is a direct thrombin inhibitor in the test system and in patients with advanced severe liver disease. The thrombin test is also positive in the presence of fibrinolysis, fibrinogen degradation products.

Test for an Inhibitor of a Coagulation Factor in the Presence of a Prolonged PT and aPTT[2]

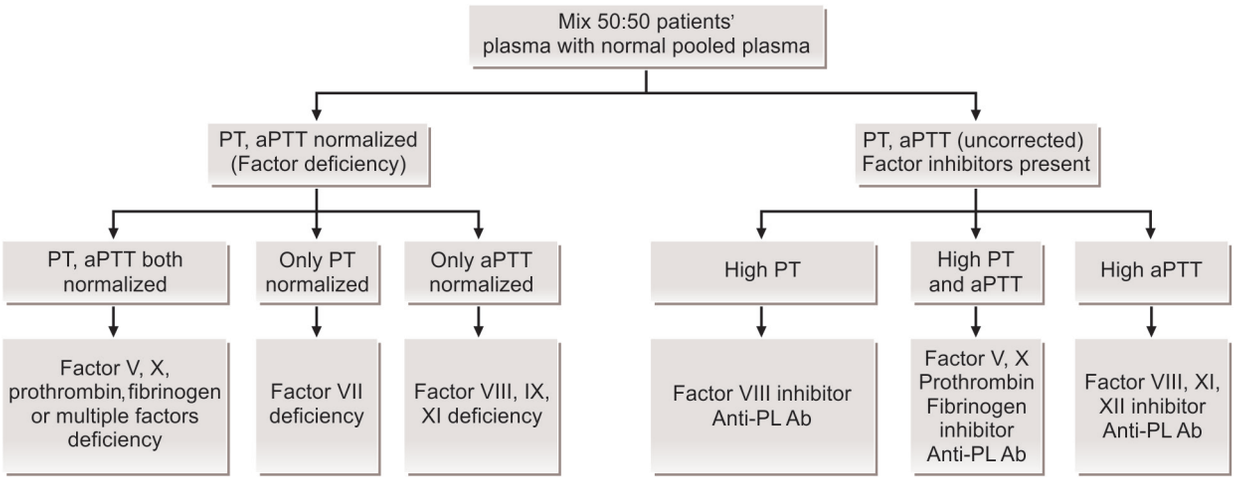
The patient's plasma is mixed with equal quantities of pooled normal plasma. The PT and aPTT are tested immediately and after 2 hours. Flowchart 1 explains the interpretation of this test.

Qualitative Platelet Defect

In the presence of normal platelet count and a Hb of at least 10 g/dL, the automatic platelet analyzer helps to detect platelet dysfunction. Special tests such as the platelet aggregation test may, however, need to be done to determine with certainty the presence and nature of platelet dysfunction.

Quantitative estimation of all coagulation factors can also be done in well-equipped specialist laboratories.

Flowchart 1: Tests to determine coagulation factor deficiency and presence of inhibitors of coagulation factors


Mix 50:50 patients' plasma with normal pooled plasma
PT, aPTT normalized (Factor deficiency)
PT, aPTT (uncorrected) Factor inhibitors present
PT, aPTT both normalized
Only PT normalized
Only aPTT normalized
High PT
High PT and aPTT
High aPTT
Factor V, X, prothrombin, fibrinogen or multiple factors deficiency
Factor VII deficiency
Factor VIII, IX, XI deficiency
Factor VIII inhibitor Anti-PL Ab
Factor V, X Prothrombin Fibrinogen inhibitor Anti-PL Ab
Factor VIII, XI, XII inhibitor Anti-PL Ab

Abbreviations: PT, prothrombin time; aPTT, activated partial thromboplastin time; Anti-PL Ab, antiphospholipid antibody.

Principles in Management

The intensivist must determine whether the hemorrhagic disorder is related to a qualitative or quantitative defect in platelets or to a coagulation disorder. Not uncommonly thrombocytopenia and/or platelet dysfunction coexist with a coagulopathy. Bleeding due to thrombocytopenia or platelet dysfunction should be treated with platelet infusions. Bleeding due to a coagulopathy should be treated by transfusion of coagulation factors through fresh frozen plasma (FFP) and/or cryoprecipitate. The nature of the coagulation defect is invariably suggested by the background disease responsible for the overall clinical problem in a given individual. Besides the routine laboratory tests stated above, a blood sample should be collected and sent to a reference laboratory for a study on qualitative platelet functions and for coagulation factor assays, if there is a detectable abnormality in the screening tests. *Treatment of the underlying disease responsible for the hemorrhagic disorder is imperative.*

Patients with bleeding or clotting disorders should not be given intramuscular injections. Blood loss should be roughly estimated and replaced. CBC and packed cell volume (PCV) should be done at necessary intervals to estimate the degree of blood loss. It may take 12–24 hours or even more, for the full effect of blood loss to manifest by a fall in the Hb or PCV, in a critically ill patient. Clinical evaluation of blood loss is therefore of prime importance.

The subsequent sections of this chapter now deal with platelet dysfunction (inherited and acquired), thrombocytopenia, and with inherited and acquired coagulation disorders.

INHERITED PLATELET DYSFUNCTION[3]

Platelets are essential for normal hemostasis. Defects in platelet adhesion, aggregation, secretion or procoagulant activity can lead to impaired hemostasis, which results in bleeding. Inherited platelet dysfunction is extremely rare, follows autosomal recessive inheritance patterns, and results in varying degrees of bleeding in neonates or in childhood. These defects are associated with a prolonged BT or absent platelet aggregation in response to platelet agonists like ristocytin, ADP, adrenaline and collagen. The coagulation profile is normal.

Bleeding associated with prolonged BT can occur with von Willebrand's disease.[4] Inherited platelet dysfunction needs to be distinguished from acquired dysfunction. Platelet aggregation studies help distinguish these two conditions. Bleeding occurring for the first time in an adult is extremely unlikely to be related to inherited platelet dysfunction.

Treatment for bleeding is the infusion of normal platelets.

ACQUIRED PLATELET DYSFUNCTION[5]

Various conditions can lead to defects in platelet adhesion, aggregation, secretion or procoagulant function without causing a significant fall in the platelet count. The most important of these are drugs. Aspirin inactivates cyclo-oxygenase and thereby prevents the production of thromboxane A_2 which mediates both platelet secretion and aggregation. Most individuals on aspirin will have a slightly prolonged BT but serious clinical bleeding is rare unless there are other hemostatic defects. However, it is always wise to stop aspirin for 5–7 days before major surgery and also before cataract surgery. Ticlopidine and clopidogrel selectively affect platelet aggregation, increase BT and may induce significant mucosal bleeds. Platelet glycoprotein IIb/IIIa inhibitors are increasingly used particularly at and after angioplasty in the management of ischemic heart disease. The use of these inhibitors is often combined with the use of anticoagulants and can at times cause catastrophic bleeding. We have seen two deaths from intracranial hemorrhage following the combined use of platelet glycoprotein inhibitors and heparin.

Acquired platelet dysfunction is common in renal failure as judged by prolonged BT (as judged by the automated plasma analyzer) and by defects in platelet aggregation.

Box 1: Important causes of qualitative platelet defects

- Associated background disease—
  - Uremia, liver cell failure
  - Myeloproliferative disorders, acute leukemia
  - Dysproteinemias
- Cardiopulmonary bypass
- Drugs—
  - Aspirin, non-steroidal anti-inflammatory drugs
  - Dipyridamole
  - Ticlopidine, clopidogrel, prasugrel
  - Platelet glycoprotein IIb/IIIa inhibitors
  - Dextrans
  - Antihistaminics, furosemide, propranolol
  - Ethanol

Remarkably enough, the risk of bleeding does not necessarily correlate with the degree of disturbance in platelet function. The exact biochemical nature of platelet dysfunction in renal failure or hepatic disease remains unknown.

Cardiopulmonary bypass induces both platelet dysfunction and thrombocytopenia. These disturbances rectify themselves within a few hours after surgery. Transient coagulation disorders also occur in the immediate postoperative period. Bleeding therefore is accentuated not only by platelet dysfunction and thrombocytopenia, but by coagulation defects and perhaps by incomplete hemostasis.

Myeloproliferative disorders, myelodysplastic syndromes, acute leukemias may result in the production of intrinsically defective platelets. Multiple myeloma, Waldenstrom's macroglobinemia are associated with the production of abnormal immunoglobulins, which can also interfere with platelet function. Important causes of acquired qualitative platelet dysfunction are listed in Box 1.

Clinical Features

The clinical features are characterized chiefly by mucosal bleeding or post-traumatic or surgical bleeding. The total platelet count is within normal limits and the coagulation profile is normal. The BT is raised. In vitro platelet aggregation studies require both experience and expertise for reliable results. They should be resorted to only in special cases with unexplained increase in BT or in patients with obscure bleeding with a normal BT and a normal coagulation profile.

Treatment

Drug-induced platelet dysfunction is treated by withdrawal of the offending drug. Desmopressin (0.3 μg/kg intravenously) is useful in the management of bleeding due to platelet dysfunction observed in uremia, liver disease and following cardiopulmonary bypass. Aprotinin, a plasmin inhibitor, is also often used to combat postoperative bleeding after cardiopulmonary bypass surgery.

Renal failure is one of the commonest causes of platelet dysfunction, and is an important cause of active serious bleeding in an ICU setting. Uremia produces a qualitative defect in platelet function, and also affects platelet adhesiveness to the capillary endothelium, by causing a defect in von Willebrand's factor. Transfused platelets may be lifesaving in severe bleeds (particularly when the bleed occurs into organ systems) in uremic patients. Cryoprecipitate (10 U)[6] and desmopressin (DDAVP) (0.3 μg/kg)[1] can both cause release of von Willebrand's factor into the circulation, and are also used to arrest the bleeding in uremia. The BT generally decreases within 1–2 hours after infusion of cryoprecipitate, and within 1–4 hours after desmopressin use. Estrogens in high doses (0.6 mg/kg per day for 5–7 days) also reduce the BT in uremic patients.[6] Bleeding in renal failure is often due to both platelet dysfunction and defects in clotting factors. The latter need to be replaced by the infusion of FFP or of appropriate coagulation factors. The bleeding tendency in patients with renal failure is decreased and more easily controlled in patients on regular dialysis and with the use of erythropoietin.

Platelet infusions should be used to counter severe bleeding due to platelet dysfunction, whatever the etiology, or for planned surgery. Drugs (in particular, aspirin) known to cause platelet dysfunction should be scrupulously avoided and the underlying disease known to cause defects in platelet function should be treated as best as possible.

THROMBOCYTOPENIA

Thrombocytopenia, i.e. a fall in the platelet count, results from decreased production of platelets in the marrow, destruction or utilization of circulating platelets or sequestration of platelets within the spleen. Important causes of thrombocytopenia are listed in Box 2. Decreased production by the marrow invariably affects all hematopoietic cells so that anemia and leukopenia are associated with thrombocytopenia. Decreased production is classically observed in extensive metastatic disease involving the marrow, lymphoproliferative diseases, myelofibrosis, myelodysplastic syndromes, aplastic anemia, and B_{12} or folic acid deficiency. Chemotherapy, exposure to radiation, drugs, and fungal, protozoal and viral sepsis can also suppress platelet production.

Increased destruction or utilization can either be mechanical or immunological. Important mechanical causes include cardiopulmonary bypass, disseminated intravascular coagulopathy (DIC), abnormal heart valves and vasculitis. Immunological destruction may result from drugs, multiple transfusions, autoimmune disease (e.g. systemic lupus erythematosus). Immune thrombocytopenic purpura is characterized by an immunological destruction of platelets occurring as an isolated disorder. Mechanical destruction of platelets is often associated with hemolytic anemia and with red blood cell (RBC) fragmentation in the peripheral smear.

Sequestration of platelets can occur in many conditions causing splenomegaly and hypersplenism. The classical example of thrombocytopenia due to hypersplenism is seen in cirrhosis of the liver with portal hypertension

Box 2: Causes of thrombocytopenia

A. *Decreased production*—
1. Marrow infiltration or replacement—
   - » Metastatic carcinoma, myelofibrosis, lymphoma, leukemia, aplasia
2. Toxic exposure—
   - » Chemotherapy, radiation, alcohol, chemicals
3. Drugs—
   - » Thiazide diuretics
4. B_{12}, folate deficiency
5. Myelodysplasia
6. Infections—
   - » Bacterial, fungal, viral, protozoal sepsis

B. *Increased destruction or utilization*—
1. Mechanical—
   - » Disseminated intravascular coagulopathy
   - » Abnormal heart valves
   - » Cardiopulmonary bypass
   - » Thrombotic thrombocytopenic purpura
   - » Hemolytic uremic syndrome
   - » Vasculitis
2. Immunological—
   - » Autoimmune thrombocytopenia
   - » Systemic lupus erythematosus, antiphospholipid syndrome
   - » Drug-induced, e.g. quinine, quinidine
   - » Chronic lymphatic leukemia, Hodgkin's lymphoma
   - » HELLP syndrome
3. Bacterial, viral, fungal and protozoal sepsis
4. Massive transfusions
5. Sequestration—hypersplenism

and splenomegaly. Anemia and leukopenia may be associated with thrombocytopenia in many patients with hypersplenism.

Clinical Features

Thrombocytopenia can cause bleeding, and the bleeding is generally from mucocutaneous surfaces. Epistaxis, bleeding gums and hematuria may occur. Petechiae are generally observed only when thrombocytopenia is marked. Spontaneous bruising is seen but soft-tissue hematomas (common in coagulation disorders) are rare in thrombocytopenia. Hemarthrosis does not occur. Severe thrombocytopenia can cause bleeding within organ systems, the most dreaded being an intracerebral bleed. Bleeding from surgical wounds, or during or immediately after surgery, is an important feature of thrombocytopenic purpura.

The risk of bleeding is, to an extent, unpredictable and depends on (1) the degree of thrombocytopenia, (2) the presence or absence of any qualitative defects in platelets, (3) the presence or absence of an associated coagulation disorder and (4) the presence or absence of associated mucosal lesions, vascular injury or trauma.

Platelet counts greater than 100,000/mm^3 do not cause bleeding. In fact surgery is safe with thrombocytopenia of this degree provided the platelets are qualitatively normal and there is no coagulation defect.

Platelet counts over 50,000/mm^3 do not cause bleeding problems, though it would be wise to avoid major surgery till the count is close to 100,000/mm^3.

Platelet counts between 30,000/mm^3 and 50,000/mm^3 generally do not cause increase in bleeding except after trauma or surgery.

When the count ranges between 20,000/mm^3 and 30,000/mm^3, the risk of spontaneous mucocutaneous bleeding increases; epistaxis, menorrhagia, hematuria and bleeding from the mouth and gums can occur.

Platelet counts below 20,000/mm^3 and particularly below 10,000/mm^3 are dangerous, can lead to severe life-threatening GI bleeds and spontaneous bleeds into viscera (e.g. intracranial hemorrhage).

Diagnosis depends on the presence of a prolonged BT, thrombocytopenia of a sufficient degree, mucocutaneous bleeding and/or petechiae, absence of other hemostatic defects and the presence of a background or associated disease known to cause thrombocytopenia.

A complete blood count and examination of the peripheral smear are important. Isolated thrombocytopenia is mostly due to an immunological cause but may occur in acute alcoholic intoxication and in hypersplenism. The presence of both nucleated RBCs and immature white blood cells in association with thrombocytopenia suggests bone marrow infiltration. Fragmented RBCs in the peripheral blood point to intravascular trauma to cells as seen with mechanical prosthetic valves, thrombotic thrombocytopenic purpura and HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome. Palpable purpuric lesions are often observed in vasculitis. Macrocytosis and pancytopenia are observed in B_{12} deficiency, particularly in strict vegetarians, whose B_{12} intake is very poor. Bone marrow aspiration and biopsy will help uncover important diseases that reduce production of platelets.

A coagulation disorder should be excluded by doing basic tests such as PT and the partial thromboplastin time (PTT). Disseminated intravascular coagulopathy is associated with an increase in both PT and PTT as also a thrombocytopenia. Other severe coagulation disorders are associated with an abnormal coagulation profile and a normal platelet count.

von Willebrand's disease or a qualitative defect in platelet function should be considered when mucosal bleeding is associated with a prolonged BT but with no thrombocytopenia.

Treatment

The principles of treatment are as follows—

- ❑ To diagnose and treat the critical illness responsible for the platelet disorder. Thus, steroids are used in idiopathic thrombocytopenic purpura or for SLE; myeloproliferative diseases responsible for thrombocytopenia merit specific treatment.

- To omit drugs which may be primarily responsible for, or which could accentuate an existing qualitative or quantitative defect in platelets.
- To replace platelets with platelet infusions.

The mere occurrence of thrombocytopenia does not merit platelet infusions. Patients do not usually bleed unless platelet counts are less than 20,000–30,000/mm^3. Platelet counts between 50,000/mm^3 and 80,000/mm^3 are generally safe for minor invasive ICU procedures, e.g. inserting or changing central lines. If surgery is necessary for a critically ill patient in the ICU, platelet levels between 80,000/mm^3 and 100,000/mm^3 are considered safe. These levels should be maintained during the surgical procedure and for 48 hours after surgery; the same levels should also be maintained during episodes of active bleeding.[7]

Platelet infusions can increase the platelet count in thrombocytopenia. Ordinarily, the infusion of one unit of platelets in an adult should produce a rise in the platelet count by 5,000–10,000/mm^3. If this increase is not observed, single-donor pheresis platelets or group-specific platelets may be given. Intravenous IgG (1 g/kg for 3–5 days) may also be given,[7] though it is effective in less than 50% of cases. Platelet infusions should preferably be given only when thrombocytopenia causes bleeding or when surgery is planned in a thrombocytopenic patient. Platelet transfusions should also be given prophylactically, particularly in critically ill individuals, whose platelet counts are less than 10,000/mm^3.

Platelet transfusions are not generally indicated in idiopathic thrombocytopenic purpura, which is treated with corticosteroids (60–80 mg prednisolone daily) and intravenous IgG. However, platelet infusions may need to be given initially to counter a life-threatening bleed in these patients. Platelet transfusions should as far as possible be avoided, and may, in fact, be harmful in thrombotic thrombocytopenic purpura, hemolytic uremic syndrome and heparin-induced thrombocytopenia.

Very occasionally heparin, which is used very frequently as an anticoagulant in the ICU, can cause thrombocytopenia, and can result in venous and even arterial thrombi. This is due to heparin-induced platelet aggregation. Thrombocytopenia (<50,000/mm^3) necessitates withdrawal of the drug, and oral anticoagulation should be substituted for heparin.

Platelet replacement by infusions has one major drawback. The half-life of platelets is short, so that within a day or two, fresh replacements are necessary. Antibodies to transfused platelets soon develop, and besides causing untoward reactions, further reduce the life-span of the transfused platelets.

INHERITED COAGULATION DISORDERS[4,8,9]

Inherited coagulation disorders are uncommon and rarely met with in a critical care unit. The pattern of inheritance is dominant or recessive, or autosomal or X-linked; rarely it results from a new mutation of a gene. In the latter instance, the family history is noncontributory to the diagnosis. A personal history often reveals previous episodes of bleeding except when the inherited defect is mild or there has been no previous challenge to hemostasis (e.g. trauma or surgery). Inherited coagulation disorders can involve any one of the several coagulation factors responsible for blood clotting. The three commonest and most important of these disorders are von Willebrand's disease, hemophilia A and hemophilia B.

von Willebrand's disease[4] results from the deficiency of von Willebrand's factor due to an inherited autosomal dominant defect in its production. This factor is essential for platelet aggregation and also serves as a carrier for procoagulant factor VIII. The disease therefore affects both platelet function and coagulation. Severe defects can cause serious bleeding similar to that observed in patients with hemophilia A.

Hemophilia A is the commonest of inherited coagulation defects and is believed to occur in 1 in 5,000 men. It is due to inheritance of an X-linked autosomal recessive mutation in the factor VIII gene that results in a mild (>5% activity), moderate (1–5% activity) or severe (<1% activity) deficiency in the production of this factor. Hemophilia is a disease of males, the female serving as the carrier. Very rarely, it may occur in females from the inheritance of two abnormal X chromosomes—one from the affected father and one from a carrier mother.

Hemophilia B results from the inheritance of an X-linked autosomal recessive mutation in the factor IX gene which results in a diminished production of factor IX. It exactly resembles hemophilia A; however, a severe deficiency of factor IX occurs only in 50% of cases. Hemophilia B is ten times less common than hemophilia A, occurring in about 1 in 50,000 men.

Inherited deficiencies of other coagulation factors are autosomal and generally recessive in nature. They are extremely rare and are observed in consanguineous marriages. Bleeding disturbances are usually not as severe as in hemophilia A and B, and, as mentioned earlier, are very rarely met with in critical care units.

Clinical Features

A careful personal history and a family history will suggest the nature of the coagulation disorder as also its pattern of inheritance.

Bleeding can occur spontaneously but it often occurs or is reported after dental extraction, trauma or surgery. In von Willebrand's disease, platelet function is also affected, so that easy bruising often occurs. In hemophilia, spontaneous bleeding from the nose, the GI tract, the urinary tract and, most importantly, into joints (hemarthrosis) is common. In patients in whom factor VIII is grossly deficient, exsanguinating hemorrhages can occur spontaneously into soft-tissues, retroperitoneally, and into various organ systems. Intracranial hemorrhage is catastrophic and generally fatal.

Laboratory Tests

Deficiency of factors II, V, VII, VIII, IX, X, XI, XII and XIII can be determined by special techniques. The diagnosis

Table 2: Principles for factor replacement in inherited coagulation disorders

Factor deficiency	*Hemostatic requirement (%)*	*Source*	*Dose*	*Interval between doses*
Factor VIII	25–30	Purified factor VIII Recombinant factor VIII	10–15 units/kg—minor bleeds 30–40 units/kg—major bleeds 10–15 units/kg—minor bleeds 40–50 units/kg—major bleeds	12 hours
Factor IX	20–30	Purified factor IX Recombinant factor IX	10–20 units/kg 100 units/kg, then 7.5 units/kg/hour	24 hours
Factor II	20–40	Fresh frozen plasma (FFP) Purified prothrombin complex concentrate (PCC)	15 mL/kg, then 5–10 mL/kg 20 units/kg, then 10 units/kg	24 hours
Factor V	15–25	FFP	20 mL/kg, then 10 mL/kg	12–24 hours
Factor VII	10–20	FFP Recombinant factor VII Purified PCC	20 mL/kg, then 10 mL/kg 60–100 µg/kg 30 units/kg, then 10 units/kg	4–6 hours
Factor X	10–20	FFP Purified PCC	15–20 mL/kg 10 units/kg	24 hours
Factor XI	10–20	FFP	15–20 mL/kg	12–24 hours
Factor XIII	3–5	FFP	5 mL/kg	1–2 weeks
Fibrinogen		Cryoprecipitate	1–2 bags/10 kg	48 hours
von Willebrand's factor	25–50	Desmopressin Cryoprecipitate	0.3 µg/kg/30 minutes 30 units/kg	24–48 hours 12 hourly for a day, then every 24 hours

of von Willebrand's disease is made on the basis of a low von Willebrand's factor antigen, an abnormal ristocetin cofactor activity and a factor VIII activity, which is generally reduced. Quantitative defects in von Willebrand's factor can be distinguished from qualitative defects by special techniques.

Differential Diagnosis

Bleeding from inherited coagulation disorders must be distinguished from bleeding caused by acquired coagulation disorders. The differentiation is evident from the history and the presence of background disease in patients with acquired coagulation defects.

It is to be remembered that abnormal coagulation tests are not always associated with bleeding. Thus, a positive lupus anticoagulant test is associated with thrombotic rather than bleeding phenomena.

Mild coagulation defects may be associated with minimally prolonged or normal coagulation tests and may result in bleeding only in the event of vascular injury.

Bleeding in the presence of normal coagulation tests suggests thrombocytopenia, or a qualitative defect in platelets, an underlying vascular defect (if there is bleeding from a single source), vasculitis, excessive fibrinolysis or factor XIII deficiency.

In patients with inherited coagulation defects, the frequent infusions of a deficient factor may induce antibodies to this factor so that subsequent infusion of this factor may not be as effective as before. Antibodies or inhibitors to factor VIII in hemophilia A can cause problems in the management of this serious disorder.

Management

Factor replacement Patients with inherited coagulation disorders need replacement of the appropriate deficient factor either when they bleed or in preparation for surgery as also in the postsurgical period (Table 2).

Surgical procedures in these patients should be performed only in centers with good laboratory facilities and good blood banks. Intramuscular injections and aspirin are avoided in patients with coagulation defects. Patients who develop inhibitors to the deficient factor can cause problems in management. The problem is usually circumvented by using larger volumes of the deficient factor as replacement therapy or by using products that bypass the factor inhibitor, e.g. activated prothrombin complex concentrate with factor VIII inhibitor bypassing activity, recombinant factor VIIa or porcine factor VIII in patients who develop inhibitors to factor VIII in hemophilia A. Plasmapheresis is at times resorted to in order to reduce the circulating inhibitory factor.

Adjuvant factors Adjuvant factors of help are desmopressin, antifibrinolytic agents (aminocaproic acid) and topical agents such as fibrin glue, and collagen preparations applied to local sites of bleeding.

Desmopressin (0.3 µg/kg intravenously over 15–30 minutes) raises both von Willebrand's factor and factor VIII to 2–5 times the prevailing level within 30 minutes. It is useful to arrest bleeding in von Willebrand's disease

and in patients with mild factor VIII deficiency. The use of desmopressin may obviate the need for factor replacement in mild bleeding episodes and may reduce the quantity of factor replacement in patients with moderate and severe bleeding episodes. It is to be noted that severe hemophilics or patients with a qualitative defect in von Willebrand's factor will not respond to desmopressin and will need factor replacement therapy.

Some units use antifibrinolytic agents as adjuncts to factor replacement therapy to control severe bleeding in inherited coagulation disorders. Contraindications to their use are the occurrence of intravascular coagulopathy or the use of prothrombin-activated complex. The dose of aminocaproic acid for the control of active bleeding is 1 g/hour till bleeding is controlled (maximum 24 g), followed by a maintenance dose of 6 g intravenously or orally every 6 hours for 7–10 days. Tranexamic acid is an antifibrinolytic agent given in a dose of 10 mg/kg intravenously or 25 mg/kg orally three to four times a day, one day before surgery or during bleeding. It should be continued for 2–7 days.

ACQUIRED COAGULATION DEFECTS

Coagulation defects in critically ill patients in the ICU are most frequently observed in liver disease, renal disease, sepsis, DIC and following massive transfusions. They may also be observed with Vitamin K deficiency. Oral anticoagulants like uniwarfarin are given in a dose sufficient to produce a controlled coagulation defect. As mentioned earlier, severe and even catastrophic bleeding can occur even when the altered clotting mechanism is within the therapeutic range. Very rarely inhibitors against various coagulation factors may develop, and lead to a serious bleeding diathesis.

From the overall clinical point of view, acquired coagulation disorders or defects are invariably characterized by deficiency of multiple factors, and are also frequently associated with thrombocytopenia and/or a qualitative defect in platelet dysfunction. The clinical features are varied and often dominated by the background disease; an abnormal coagulopathy is just one manifestation of this underlying disease process.

Clinical Diagnosis

A good clinical history, physical examination and basic laboratory screening tests to determine the coagulation profile generally suffice to help diagnose the nature of the coagulation defect.

The clinical features are characterized by bleeding, the presence of background disease known to cause an acquired coagulation defect and the laboratory evidence of a coagulation disorder.

Bleeding can be spontaneous, or excessive bleeding may result from surgical procedures. A disruption of vascular or mucosal integrity can lead to profuse bleeding. This is particularly observed in cirrhotics with varices due to portal hypertension or those with one or more mucosal ulcers in the GI tract. These patients bleed profusely into the gut and present with exsanguinating hematemesis or melena.

Spontaneous bleeding may occur from the mucosa at various sites, can result in bruising of the skin, soft-tissue hematomas, retroperitoneal hematomas, and hematomas or bleeds into organ systems. However, petechiae so often seen in severe thrombocytopenia or platelet dysfunction do not generally occur in patients with acquired coagulation defects.

Disseminated intravascular coagulopathy is one condition in which bleeding may be associated clinically with intravascular thrombosis in various organ systems.

A brief resumé of the nature of clotting defects found in the clinical conditions mentioned earlier is given below.

Liver Disease[10,11]

Multiple coagulation abnormalities are invariably present in patients with advanced liver cell dysfunction. The liver synthesizes all coagulation factors except factor VIII and von Willebrand's factor. It also synthesizes other regulatory proteins including α_1 antiplasmin, protein C, protein S and antithrombin III. The liver is responsible for the clearance of activated clotting factors, and the degradation products of fibrin and fibrinogen. Liver dysfunction prevents Vitamin K from being effective in the synthesis of Vitamin K-dependent clotting factors resulting in a functional Vitamin K deficiency. There is also impaired fibrin polymerization due to increased fibrin degradation products and accelerated fibrinolysis. Finally, thrombocytopenia or a qualitative defect in platelet function may be associated with the coagulation abnormalities described above.

Bleeding in severe liver disease is therefore multifactorial and is invariably due to a deficiency of several coagulation factors. The PT is elevated; it is a sensitive index of liver cell function. Later the aPTT is also prolonged due to low levels of factors IX and X. Patients with severe liver disease cannot utilize Vitamin K; the PT therefore remains high and unchanged after Vitamin K therapy. The decreased levels of protein C and a decreased clearance of activated clotting factors predispose to the development of DIC. The accelerated fibrinolysis, and the associated thrombocytopenia and platelet dysfunction can contribute strongly to bleeding in some patients.

Treatment of severe bleeding in liver disease may be individualized according to the deficiency of one or more factors, as evinced from a study of the coagulation profile. This may not be possible if an elegant sophisticated laboratory back-up is unavailable. In any case, acute bleeding necessitates urgent replacement of clotting factors. This is best achieved by infusion of FFP. Six to ten units of FFP may have to be infused to raise the clotting factors to a level that arrests the hemorrhage. The short half-life of clotting factors necessitates frequent use of FFP, which may easily precipitate a fluid overload in critically ill patients. When patients cannot tolerate the large volume of FFP necessary to stop the bleed, exchange transfusions with replacement by FFP may be life-saving. Continuous arteriovenous hemofiltration is an

alternative method of reducing fluid overload in such patients. An infusion of cryoprecipitate (8–10 units) becomes necessary when the fibrinogen level falls close to or below 100 mg/dL.

Platelet transfusions may also be necessary because of quantitative or possible severe qualitative defects observed in liver cell dysfunction. Thrombocytopenia in chronic liver cell disease is however often due to hypersplenism. In these patients platelet infusions do not produce the expected increase in the platelet count.

Factor IX concentrates (activated prothrombin complex concentrates), which are rich in Vitamin K-dependent factors, can be selectively used to counter hemorrhage in acute hepatocellular failure. The main advantage is a reduced volume load. The disadvantages are the risk of blood borne viral infections and of thrombotic complications including DIC.

Prophylactic infusions of FFP or of selective clotting factors found to be deficient in patients with liver disease, may need to be given before any emergency or elective major surgery.

Renal Disease[6]

Uremia in renal failure very frequently produces platelet dysfunction and a deficiency of clotting factors. Management of platelet dysfunction has been outlined earlier. Clotting factors are replaced by FFP, or by selective replacement of one or more deficient factors. Hemodialysis improves bleeding tendencies in renal failure. In the presence of acute bleeding requiring emergency infusions of large volumes of FFP and of packed RBCs, a continuous arteriovenous hemofiltration is necessary to avoid fluid overload.

Disseminated Intravascular Coagulopathy[12-16]

Disseminated intravascular coagulopathy occurs as a result of abnormal activation of coagulation and clotting factors because of vascular injury, release of precoagulant factors into the blood or both. This leads to consumption of coagulation factors (consumption coagulopathy), and of platelets, and is accompanied secondarily by increased fibrinolysis. A generalized bleeding tendency results with bleeding from the mucosa, puncture sites and surgical wounds. The clinical spectrum ranges from small thrombi in multiple organ systems that can result in organ dysfunction on the one hand, to profuse bleeding on the other. Evidence of both thrombi and active bleeding may be present. The presence of small thrombi in the microcirculation leads to tissue hypoxia. Widespread thrombi together with bleeding produce the features of purpura fulminans, with skin necrosis and gangrene of fingers and toes, or even of distal portions of the extremities. Multiple organ dysfunction chiefly involves the kidneys, liver, lungs, skin and the central nervous system.

There are numerous causes of DIC. The most important cause is bacterial sepsis, and in tropical countries, fulminant *Plasmodium falciparum* infections. Other fulminant infections can also produce a DIC. The next most common cause observed by us in our setting is the presence of obstetric complications—in particular eclampsia, retained dead fetus and abruptio placenta. In Southern India, and in other snake-infested regions of the world, viper bites are an important cause of DIC. Severe burns, crush injuries, trauma, malignancies and acute leukemias are other conditions causing DIC. A consumption coagulopathy should always be suspected whenever there is bleeding or evidence of thrombotic episodes or both, in the clinical conditions given in Box 3.

Box 3: Important background diseases causing disseminated intravascular coagulopathy in the ICU

- Infections: bacterial, fungal, viral, protozoal, e.g. *P. falciparum* infection
- Obstetric complications: ectopic pregnancy, abruptio placenta, retained dead fetus, septic abortion, amniotic fluid embolism
- Massive trauma, crush injuries
- Burns
- Snake bite
- Neoplasms, acute leukemias
- Vascular disorders, presence of prosthetic devices, giant hemangiomas, aortic aneurysm
- Miscellaneous causes, e.g. acute lung injury, acute pancreatitis, blood transfusions, hyperthermia, hypothermia, severe hypotension, hypoxia

The laboratory diagnosis of DIC is not always easy. In low-grade DIC, the synthesis of coagulation factors and platelet production keep pace with the increased consumption. Screening coagulation studies may be normal in these patients. The only laboratory abnormality may be a rise in the fibrin degradation products.

In the more severe form of DIC that is generally observed in an ICU setting, bleeding is invariably present. The patients show a prolonged PT and PTT, thrombocytopenia, hypofibrinogenemia and increased fibrin degradation products. None of these tests are sensitive or specific enough to conclusively establish a diagnosis of DIC. Coagulation defects in severe liver disease may at times be impossibly difficult to differentiate from those in DIC. The factor VIII levels are generally not significantly diminished in liver cell failure, but are severely decreased in DIC. Also, the presence of circulating fibrin monomers as judged by a positive protamine sulfate test or the presence of cross-linked fibrin as judged from a positive D-dimer test generally points to DIC.

Schistocytes (fragmented RBCs) may be found in patients with DIC. When present, DIC should be distinguished from microangiopathic hemolytic anemia. The latter condition is observed in thrombotic thrombocytopenic purpura, hemolytic uremic syndrome and the HELLP syndrome. Microangiopathic hemolytic anemia is however characterized by hemolytic anemia, fragmented RBCs in the blood smear, thrombocytopenia, without alteration of the coagulation profile. It can therefore be distinguished from DIC.

In the final analysis, it is the clinical background which prompts the diagnosis of DIC in a critically ill, bleeding patient, who has an elevated PT, a reduced platelet count and an increase in the serum levels of fibrin degradation products.

Management

Disseminated intravascular coagulopathy is a manifestation of a serious underlying disorder, and management should always be primarily directed towards the disease. Sepsis needs to be countered by appropriate antibiotics, and surgical drainage or intervention should be promptly instituted whenever indicated.

Serious bleeding is countered by fresh blood transfusions and by transfusions of FFP in sufficient quantity so as to decrease the PT to within 2–3 seconds of normal. Cryoprecipitate may be infused to maintain fibrinogen levels above 100 mg/dL and platelet concentrates given to raise the platelet count to greater than 50,000/mm^3. Unfortunately, as stated earlier, both platelets and clotting factors have a short half-life, so that the effects of these infusions are very transient. We have never used heparin in DIC. Its use in lower doses has been advocated in purpura fulminans, in DIC complicating acute leukemia and in patients with low-grade DIC due to solid tumors manifesting as small widespread thrombi in various organs of the body. Secondary fibrinolysis invariably accompanies DIC. Antifibrinolytic agents are generally contraindicated because of the risk of inducing widespread thrombosis. Some units however persist with the use of epsilon-aminocaproic acid in patients with severe fibrinolysis and with no evidence of thrombotic complications.

It should be noted that massive external or internal bleeding can cause a consumption of clotting factors and mimic DIC. In this situation, though the consumption and depletion of clotting factors and platelets may result in a serious increase in bleeding tendency and a rise in the fibrin degradation products, formation of thrombi in the microvasculature of various organ systems does not occur.

Primary fibrinolysis is a very rare bleeding disorder and results in a rapid dissolution of fibrin clots, destruction of fibrinogen and consumption of plasminogen and its inactivators. It has to be distinguished from DIC. Primary fibrinolysis is not associated with intravascular thrombi nor with thrombocytopenia.

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Massive Transfusions[17]

Patients receiving large volumes of blood in the form of packed RBCs or stored whole blood will develop thrombocytopenia and a deficiency of labile clotting factors. Platelet infusions must be given to these patients to maintain a platelet count close to 100,000/mm^3, and FFP is infused to counter Factors V, VIII, and other clotting factor deficiencies. If necessary, cryoprecipitate should also be infused to maintain fibrinogen levels above 100 mg/dL. Usually, 1 unit of FFP is given after every 4 units of packed RBCs, and 4–6 units of platelets after every 10 units of packed RBCs. If the patient continues to bleed in spite of adequate replacement, other causes for bleeding should be sought. Local pathologies in the gut, notably stress ulcers, are often responsible for severe GI bleeding. Bleeding in patients, who have sustained severe traumatic injuries or who have been in shock due to poor tissue perfusion, could be due to a DIC.

Vitamin K Deficiency

Vitamin K is necessary for the synthesis of a number of clotting factors—Factors II (prothrombin), VII, IX, X and Proteins C and S. This vitamin is present in green vegetables, and is also synthesized by bacteria in the intestinal lumen. Vitamin K deficiency occurs in seriously ill patients, particularly when they are on broad-spectrum antibiotics. Obstructive jaundice can also lead to vitamin K deficiency. Malabsorption from any cause does the same. Patients on oral anticoagulants (like warfarin) have an induced vitamin K deficiency, as these anticoagulants inhibit its metabolism in the liver. Aspirin in high doses as well as certain cephalosporins are known to induce a deficiency of vitamin K-dependent coagulation factors; this can be reversed by administration of vitamin K.

Vitamin K deficiency results in a deficiency of all vitamin K-dependent clotting factors. Factor VII is depleted first because it has the shortest half-life. This leads to an increase in the PT. Factors IX and X are depleted next, causing an increase in the activated PTT. If the patient's liver function is normal, vitamin K_1 given as an intravenous infusion over 10–15 minutes will normalize the PT in 6–24 hours and the PTT in 24–48 hours. Parenteral vitamin K_1 reverses the effects of oral anticoagulants like warfarin, in the same period of time. If correction of PT does not occur within 24–48 hours, liver functions are invariably deranged. In severe bleeding resulting from vitamin K deficiency, FFP should be administered in addition to vitamin K to help increase the levels of depleted clotting factors.

DRUGS

- *Warfarin* is the most frequently used anticoagulant. It should be monitored by doing the PT at periodic intervals, the international normalized ratio (INR) being kept between 2 and 3. Rarely serious bleeding can occur even when the PT is within the therapeutic range. If the INR exceeds normal but is below 5 and the patient does not bleed, it is best to withhold the drug till INR falls in the therapeutic range and then restart a titrated dose of the drug. If the INR is between 5 and 9, and there is no bleeding, the drug is withheld, and if there is a serious risk for a possible bleed, 1 mg vitamin K is given intravenously or 5 mg given orally and repeated if necessary, after 24 hours. If the INR is greater than 9, 2.5 mg vitamin K is given IV repeated, if necessary, after 12–24 hours. If there is a serious bleed after the use of warfarin, with prolongation of the INR, IV 10 mg vitamin K is given over 10 minutes. FFP, prothrombin complex concentrate or factor VIIa will enable prompt reversal of the anticoagulant effect.

Table 3: Laboratory findings in acquired coagulation disorders

	DIC	*Liver disease*	*Kidney disease*	*Vitamin K deficiency*	*Inhibitors*	*Primary fibrinolysis*
PT prolonged	+	+	+	+	+	
PTT prolonged	+	+	+	+	+	
TT prolonged	+	+				+
FDP elevated	+	+			+	+
D-dimer present	+	+				
Protein C/S diminished	+	+		+		
Antithrombin III diminished	+	+				
Fibrinogen diminished	+	+				+
Associated thrombocytopenia	+	+				
Red blood cells	Schistocytes present	Target cells, macrocytes present	Schistocytes present			

Inhibitor screen: Mix with normal plasma. If no correction—inhibitor present
If correction—factor deficient
The coagulation profile in severe liver disease is very similar to that in DIC; however, in liver disease, the factor VIII levels are not significantly reduced, while in DIC, they are severely reduced.

- *Heparin*, low molecular weight heparin and fondaparinux are anticoagulants which need to be monitored (aPTT and factor Xa). *Bleeding is countered by the administration of IV FFP. Bleeding due to unfractionated heparin can be countered by the use of IV protamine and infusion of FFPs. Bleeding following the use of low molecular weight heparin can be only partially countered by IV protamine. Recombinant factor VII (rVIIA) should be given in patients with severe bleeding. There is no antidote to bleeding caused by Factor XA inhibitors like fondaparinux. Severe life-threatening bleeds should be countered by the infusion of rVIIA.*
- Direct thrombin inhibitors include *argatroban, lepirudin* and *bivalirudin*. There is no antidote for bleeding caused by these drugs. Fortunately, they have a short half-life, so that bleeding spontaneously stops with time. *Cryoprecipitate, antifibrinolytics and desmopressin acetate should be administered for life-threatening bleeds (see Table 6 in Chapter Pulmonary Embolism).*
- Superwarfarins are present in rat poison, which is occasionally taken with suicidal intent. The bleeding is severe and persistent as the raised PT remains very high for days or weeks.

CIRCULATING INHIBITORS TO COAGULATION FACTORS

Circulating inhibitors pose significant problems in the management of bleeding disorders. As with the treatment of hemophilia A, management consists of using high doses of the particular deficient coagulant factor or using factors that bypass the factor that is being inhibited (use of activated prothrombin complex or recombinant factor VIIa). The titer of the inhibitor factor can be reduced by plasmapheresis or by immunosuppression. In patients with multiple myeloma, the abnormal myeloma protein prevents fibrin polymerization. Chemotherapy against myeloma can rectify this abnormality; plasmapheresis is useful as a temporary measure.

Table 3 gives important laboratory findings in acquired coagulation disorders.

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CHAPTER 58

Transfusion (Blood Product) Therapy

INTRODUCTION

Whole blood or blood products are of extreme therapeutic value in critical care units. However, despite all care and attention in the collection, preparation and storage of blood products, there is an inherent risk in the administration of these products. The benefits in appropriate clinical settings invariably outweigh the risks. Even so, the hazards of transfusions should always be borne in mind, so that blood products are only transfused when absolutely indicated.

This chapter gives the blood components available for transfusion, indications for use and their therapeutic effects. It then goes on to briefly describe complications of transfusion, including the risk of transmitted infection, and various transfusion reactions encountered in clinical practice.

BLOOD PRODUCTS[1,2]

The text below outlines the blood products available and indications for their use (Table 1).

Red Blood Cells[1-4]

Red blood cell concentrates are prepared by removing most of the plasma from a unit of whole blood. This is the blood product of choice when increase in the oxygen carrying capacity of blood is desired, as in an anemic patient. Each unit contains 200–225 mL of red cells, and should raise the hematocrit by 3%. In a bleeding patient, who is given packed RBCs, volume replacement should be supplemented by infusion of colloids or crystalloids. Besides acute blood loss, RBC transfusions are indicated in severe anemia. The decision to transfuse cells is based not only on the hematocrit or Hb value, but also on the clinical state of the patient.

In the intensive care unit, anemia is an important frequently encountered problem and can be due to several causes. In the critically ill patient, adequate tissue oxygenation is of vital importance. Oxygen delivery and oxygen consumption by tissues can be impaired if there is a reduced cardiac output (a fall in O_2 delivery), decreased red cell mass (lowered Hb) and a decrease in the circulating volume caused by RBC loss or reduction. Besides overt or occult blood loss, anemia in this setting could be due to other causes, which include hemolysis, inability to utilize iron, impaired haemopoiesis in the marrow and decreased erythropoietin production.

Infusion of packed RBCs increases the oxygen carrying capacity of blood and increases oxygen delivery to the tissues. This is all to the good in critically ill anemic patients, but the question that arises is at what level of Hb does one transfuse a critically ill patient.

There exists a considerable variability in transfusion parameters and in spite of guidelines from different centers, the treatment of anemia in critically ill ICU patients is not yet well-defined. One view advocates RBC transfusions if the Hb is less than 10 g/dL; another more "restrictive" approach is to transfuse only when Hb is less than 7 g/dL, keeping the Hb between 7 g/dL and 9 g/dL. The latter view suggests that Hb values between 7 g/dL and 9 g/dL are well tolerated by critically ill patients. Admittedly there is evidence to support the "restrictive" approach. In a large multicenter randomized trial, patients transfused at an Hb threshold of 10 g/dL had a higher mortality than those transfused at an Hb threshold of 7 g/dL.[5] Advocates of a restrictive transfusion strategy[6] maintain that trying to achieve a normal or near normal Hb concentration does not improve mortality in critically ill patients and may be associated with increased risk of infection and increased morbidity and mortality. The exception to the

Table 1: Commonly available blood products and main indications for their use

Blood product	*Main indications*
Red blood cells (RBCs)	Restoration of oxygen carrying capacity
Whole blood	Restoration of oxygen carrying capacity + restoration of blood volume
Leukocyte-poor red cells	Restoration of oxygen carrying capacity, prevention of febrile transfusion reactions
Frozen/Deglycerolized red cells	Used in patients who are extremely sensitive to plasma, e.g. those with congenital absence or marked deficiency of immunoglobulin A (IgA).
Platelets	Actively bleeding patient with thrombocytopenia, thrombocytopenic patient undergoing surgery, prophylactically in patients with platelet count less than 10,000/mm^3
Leukocytes	In patients having neutropenia with sepsis; hardly ever used. The granulocyte-stimulating factor is more effective
Fresh frozen plasma (FFP)	Replacement of multiple coagulation factor deficiencies, e.g. in patients with uremia, liver disorders, disseminated intravascular coagulation (DIC), and following multiple blood transfusions
Cryoprecipitate	Hemophilia A, von Willebrand's disease, Hypofibrinogenemia
Specific clotting factors— • Factor VIII concentrate • Prothrombin complex concentrate	 Hemophilia A Deficiency of factor II, VII, IX or X
Factor VIIa	Bleeding in hemophilia A + exsanguinating life-threatening bleeding from other causes
Other blood products— • Human albumin • Intravenous (IV) immunoglobulin	 Expansion of plasma volume as in burns, to increase serum albumin levels in patients with hypoalbuminemia In patients with immune thrombocytopenic purpura (ITP), or congenital deficiency of immunoglobulin

above restrictive policy is with regard to patients who have an acute coronary syndrome. In these patients the, Hb should be close to 10 g/dL. On the other hand, those advocating a more "liberal" transfusion policy stress on the possible dangerous effects associated with an increasing oxygen debt.[7]

Though many critical care units follow the "restrictive approach" to blood transfusions in critically ill patients, it is important to consider each patient's requirements individually rather than apply a blanket rule based on the statistical analysis of randomized controlled trials involving large population groups. It is important to remember that the heart and brain are extremely vulnerable to the lack of oxygen. Elderly people with a history of myocardial infarction, patients with documented multivessel coronary disease, those with a history of a stroke in the recent past or a history of recurrent transient ischemic attacks perhaps deserve a less "restricted" policy toward transfusion of RBCs. It is impossible in a critically ill elderly individual to assess the state of the coronary arteries or the cerebral vessels. An electrocardiography (ECG) is certainly no guide to the presence or absence of coronary artery disease. In all the above situations, it may perhaps be wise (notwithstanding the absence of "evidence") to keep the Hb close to 10 g/dL.

It should be noted that any condition that impairs the ability of the patient to increase stroke volume, cardiac output and intravascular volume will result in poor tolerance of acute blood loss or severe anemia. Patients with ischemic heart disease or poor pump function may be unable to maintain satisfactory tissue perfusion to the myocardium and to other vital organs after blood loss and may need more urgent yet carefully administered packed RBC transfusions. Patients with respiratory disease and a PaO_2 less than 55 mm Hg require urgent replacement of blood loss as the lowered PaO_2 coupled with a low Hb produce a sharp fall in the O_2 content of blood. Patients with chronic liver disease are tipped into liver cell failure with even a minor blood loss in the GI tract, and often need prompt transfusions to replace the blood lost. In all the above conditions, each patient should be judged individually, and, if thought appropriate, the restrictive approach may need to be a trifle relaxed. Yet it needs to be pointed out that a Hb greater than 10 g/dL is of no advantage and can perhaps even do more harm than good.

In the acutely bleeding patient, who runs a risk of dying due to exsanguination within a short time, un-crossmatched O-negative red cells may be transfused till properly typed and cross-matched blood is available. It needs to be stressed that infusions of packed RBCs are not the right choice to augment blood volume at a quicker rate. The use of crystalloids, colloids or whole blood is preferable for this purpose (see Chapter Hypovolemic and Hemorrhagic Shock).

Whole Blood

Whole blood contains both RBCs and plasma. Transfusion of whole blood increases both the oxygen carrying capacity of blood, as also the volume. Whole blood is to be preferred in the severely bleeding patient, and, when transfused, it should

be ABO identical with that of the patient. The use of whole blood in a patient, who is not bleeding profusely, exposes the patient unnecessarily to plasma, and prevents donor blood from being processed into other blood components. Platelets and clotting factors, particularly factors V and VII, are not adequate in whole blood.

Gamma-irradiated Blood

The application of external beam radiation to a unit of blood produces gamma-radiated blood. This allows for destruction of donor T lymphocytes for the prevention of graft versus host disease in patients who have undergone stem cell transplant and in severely immunocompromised patients.

Cytomegalovirus Antibody Negative Blood

Cytomegalovirus (CMV) antibody negative blood is used in patients (e.g. transplant recipients) who are CMV negative and are therefore at high risk if transfused with CMV positive blood. Leukocyte reduction is also an effective method to reduce risk of CMV infection.

Leukocyte-poor Red Cells

This product is prepared in a manner that eliminates most leukocytes and platelets, but retains at least 80% of the RBCs. The leukocyte count is less than 5×10^8 per unit. The method of preparation of leukocyte-poor red cells is by centrifugation and washing, or by more elaborate filtration methods. Filters and filtration methods, if available, are now more frequently used in well-equipped blood banks. Leukocyte-poor red cells are valuable in patients who have recurrent febrile reactions after transfusion of the usual packed RBCs. Such reactions are believed to be caused by sensitization to human leukocyte antigen (HLA) present in donor leukocytes, as also to other surface antigens on leukocytes and platelets in donor blood. Such sensitization is common in patients receiving multiple blood transfusions. The advantage of leukocyte and platelet-free RBCs is twofold: (1) it reduces the incidence of HLA alloimmunization caused by blood products and (2) it reduces (but does not completely eliminate) the risk of transmission of CMV from the donor to the recipient.

Frozen/Deglycerolized Red Cells

Red cells can be frozen and stored if glycerol is used as an intracellular cryoprecipitant. When they need to be used, the red cells are thawed, and the glycerol removed by extensive washing, a process that removes all plasma, leukocytes and platelets. This product is used for patients who are known to be extremely sensitive to plasma, as in those who have a congenital absence or marked deficiency of IgA. Ordinary packed cells or whole blood transfusions can cause almost life-threatening reactions in IgA-deficient patients. Frozen/deglycerolized RBCs are difficult to obtain, extremely expensive to prepare and store, and have no additional advantage for routine use.

Platelet Transfusions[1,2,8]

Platelet transfusions can control bleeding in patients with severe thrombocytopenia or in those with qualitative defects in platelet function. One unit of blood ordinarily yields platelets sufficient to raise the platelet count by about 10,000/mm^3 per square meter of body surface area. This amounts to a rise of 5,000–7,000 platelets/mm^3 in a 70 kg adult. Ordinarily, 6–8 units of platelets are administered to produce a significant rise in the platelet count. It is necessary to do a platelet count 1 hour and 24 hours after transfusion, so that the effectiveness of the transfusion in raising the platelet count can be estimated. Antibodies to platelets from alloimmunization can lead to rapid destruction of transfused platelets. Fever, sepsis, drugs, liver cell dysfunction, uremia and hypersplenism probably shorten even further the life-span of transfused platelets.

The indications for platelet transfusions, which have been briefly touched upon earlier, are recapitulated below—

- The actively bleeding patient with thrombocytopenia. A platelet count of 50,000/mm^3 in these patients generally ensures hemostasis unless there is a co-existing qualitative defect in platelet function.
- Usually, spontaneous bleeding does not occur until the platelet count falls below 5,000–10,000/mm^3. Prophylactic platelet transfusions are generally given in patients undergoing chemotherapy or hematopoietic stem cell transplant if the platelet count is less than 10,000/mm^3 even in the absence of bleeding.
- For elective or emergency surgery or high-risk procedures in patients with thrombocytopenia, platelet infusions are necessary to raise the platelet count to greater than or equal to 100,000/mm^3. This level should be maintained for at least 48 hours after surgery.
- For the majority of invasive procedures performed in the ICU (insertions of central lines, pleural or peritoneal tap, etc.), a platelet count of 30,000–50,000 is adequate.
- Alloimmunization to platelet antigens often results in poor survival of transfused platelets, and a poor response is inevitable. HLA-matching can improve platelet survival in 70% of alloimmunized patients. Obtaining HLA-matched platelets is difficult because of the heterogenicity of HLA antigens, and requires technicians and doctors with experience and expertise.
- Platelets are of no use in the treatment of bleeding due to idiopathic thrombocytopenic purpura, a condition in which there is autoimmunization to platelet antigens. These patients need specific treatment with corticosteroids. It is remarkable how counts as low as 5,000–10,000/mm^3 are tolerated without active bleeding in these patients. This is perhaps related to the production of young "extra sticky" platelets by the bone marrow. These platelets are very effective in securing hemostasis during their short period of survival.
- Desmopressin administered intravenously increases the level of von Willebrand's factor; this improves platelet function in uremia and following cardiopulmonary bypass.

- Platelet counts less than 50,000/μL are associated with increased rate of microvascular bleeding in the massively transfused patient. Therefore, platelet transfusions have been advocated with replacement of blood volume to avoid dilutional thrombocythemia.
- A qualitative defect in platelet function can induce bleeding even when the platelet count appears adequate. Platelet transfusions are indicated in these patients. Platelet function abnormalities are observed after use of certain drugs, in sepsis, trauma, malignancy, in obstetric complications, hepatic and renal disease. The use of glycoprotein IIb IIIa inhibitors in patients with ischemic heart disease leads to a qualitative defect in platelet function with bleeding as a recognized complication.
- The expected rise in the platelet count following platelet infusion is as follows—
  - One unit in a 50 kg individual will cause a rise of 9,000/μL; 6 units a rise of 54,000/μL.
  - One unit in a 70 kg individual will cause a rise of 6,000/μL; 6 units a rise of 36,000/μL, provided the spleen is normal and there are no platelet antibodies.

Fresh Frozen Plasma[1,2,8]

Fresh frozen plasma (FFP) is prepared from whole blood, and is frozen within 6 hours of collection of the donated unit. Each unit of FFP contains 250 mL plasma, all the clotting factors, and 400 mg of fibrinogen. FFP infusions are indicated to replenish deficiency of multiple clotting factors as observed in uremia, liver disease, DIC and coagulopathy following multiple blood transfusions. FFP (together with intravenous vitamin K) is also useful in reversing the coagulopathy produced by warfarin, and may be beneficial in treating thrombotic thrombocytopenic purpura and antithrombin III deficiency.

One unit of FFP increases the level of clotting factors by 3% in an adult. Excessive bleeding is controlled and generally stops when clotting factor levels are over 30% and the prothrombin time (PT) and partial thromboplastin time (PTT) are reduced to about 1.5 times normal. It is therefore not necessary to aim at restoring clotting factors to absolute normal levels. The efficacy of FFP infusions should be monitored by coagulation assays—at least of the PT and the PTT. Specific factor deficiencies may be treated by infusion of specific factors. The short half-life of clotting factors and the dangers of fluid overload need to be kept in mind.

Cryoprecipitate[1,2,8]

When FFP is thawed at 4°C, a precipitate is formed. This cryoprecipitate is separated from the supernatant plasma, re-suspended in a small volume of plasma, and then refrozen at −18°C. The cryoprecipitate can be stored for a year. Each bag or unit of cryoprecipitate (about 50 mL) contains 100–250 mg fibrinogen, 80–100 units of factor VIII, 40–70% of von Willebrand's factor concentrate, and factor XIII in a concentration 2–4 times that present in FFP.

Cryoprecipitate transfusions are indicated in bleeding due to severe hypofibrinogenemia (<100 mg/dL), in patients with deficiency of von Willebrand's factor, in hemophilia and in factor XIII deficiency. It is particularly useful in achieving hemostasis in patients with uremia or chronic liver disease with low serum fibrinogen levels and in patients with DIC.

Fibrinogen levels should be kept greater than 100 mg/dL to counter bleeding due to fibrinogen deficiency. Two to three bags of cryoprecipitate per 10 kg will raise fibrinogen concentration by about 100 mg/dL. Maintenance doses of 1 bag/15 kg body weight can be given daily till the bleeding is controlled. Bleeding due to deficiency of von Willebrand's factor stops if this factor level is increased to 50%, and the prolonged BT is corrected. Factor XIII replacement requires transfusion of 4–6 bags of cryoprecipitate every 3 weeks.

Specific Clotting Factors[1,2,8,9]

Factor VIII concentrate and factor IX (prothrombin complex) concentrate are prepared by fractionation and lyophilization of pooled plasma. Factor VIII is used in the treatment of hemophilia A. It is not used in an intensive care setting except for bleeding hemophilics requiring critical care. All current methods of preparing factor VIII inactivate the human immunodeficiency virus (HIV I), and decrease the incidence of transmission of Non-A, Non-B hepatitis. Bleeding hemophilics, who have antibodies to factor VIII, can be given porcine factor VIII concentrate, or activated prothrombin complex concentrates that bypass factor VIII in the coagulation cascade.

Factor IX concentrates contain factors II, VII, IX and X, and can be used in patients with selective deficiency of these factors.

Factor VIIa[9] is a recombinant factor and is used for bleeding complications in hemophilia with inhibitors to factor VIII, in acquired hemophilia A and B, and in factor VII deficiency. Severe exsanguinating bleeding, which is life-threatening, is another indication for infusion of factor VIIa, provided it is ascertained that there is no local cause for the bleed and the use of FFP, cryoprecipitate has been ineffective. The dose of factor VIIa in the above situation is 60 μg/kg IV; this can be repeated after 2 hours if the bleeding has not stopped. Thrombotic complications are known to occur after its use.

Other Blood Products

These are prepared by fractionation of large pools of plasma. They include intravenous immunoglobulin used to treat congenital immunoglobulin deficiency and idiopathic thrombocytopenic purpura.

Intravenous human albumin preparations are chiefly indicated in hypovolemic states (e.g. burns) to expand the volume of the vascular compartment and thereby support circulation. They are also used to increase serum albumin levels in patients with marked hypoalbuminemia. Very low serum albumin levels can lead to waterlogging of tissues and is a bad prognostic sign in a critical illness.

Table 2: Important immune-mediated acute transfusion reactions

Reaction	*Symptoms*	*Etiology*
Anaphylactic	Choking in throat, bronchial spasm, constricting chest pain, anxiety and shock	Antibodies to donor plasma proteins (severe); often anti-immunoglobulin A (IgA)
Transfusion-related acute lung injury (TRALI)	Dyspnea, tachypnea, fever, hypoxia, tachycardia and bilateral pulmonary infiltrates	Antibodies to donor leukocytes or antibodies in a donor reacting with recipient HLA or leukocyte-specific antigen
Acute hemolytic	Fever, flank pain, chest tightness, shock, hypotension, oliguria and renal shut-down	Antibodies to donor red cell antigens

TRANSFUSION REACTIONS

Transfusion reactions occur in about 5% of patients. They may be very mild and permit continuation and completion of the transfusion; occasionally they may be severe and life-threatening, necessitating immediate stoppage of the transfusion and institution of emergency measures to counter these reactions.

The important immune-mediated transfusion reactions are summarized in Table 2.

Anaphylactic Reactions

These are frightening. A choking feeling in the throat, constricting chest pain, and a state of shock quickly supervene. Overwhelming bronchial spasm may choke the patient to death within a few minutes. The transfusion should be stopped immediately. Adrenaline 0.5 mL intramuscular or intravenous is administered and is followed by 300 mg of intravenous hydrocortisone. The airway should be secured, and oxygen administered at a high flow rate. Circulatory support with volume infusions and inotropes are necessary. The blood bank should be immediately informed about the untoward reaction.

Transfusion-related Acute Lung Injury[10]

Transfusion-related acute lung injury (TRALI) is an extremely distressing complication occurring within 30 minutes to 6 hours after transfusion. It is characterized by sudden onset of dyspnea, fever, tachypnea, tachycardia, hypoxia with bilateral pulmonary infiltrates most marked in the mid and lower zones of both the lungs. Bilateral basal crackles are heard on auscultation. The condition resembles acute respiratory distress syndrome (ARDS), or volume overload, or acute left ventricular failure. It is due to non-cardiogenic pulmonary edema due to a capillary leak within the pulmonary vessels. It is believed to be an immune-mediated process due to antibodies present in the donor blood reacting with recipient HLA or leukocyte-specific antigen. Alternatively, the recipient, i.e. the patient, could have antibodies reacting against the donor leukocytes. A nonimmune mechanism has also been postulated.

The treatment is supportive. High flow oxygen is administered. In most cases TRALI is self-limiting, but mechanical ventilatory support is occasionally necessary.

Febrile Non-hemolytic Transfusion Reactions

Febrile non-hemolytic transfusion reaction (FNHTR) is a 1°C or greater rise in temperature, which cannot be explained by the patient's clinical condition. FNHTR is generally due to sensitization to the antigen on donor leukocytes. It is more common with platelet transfusion or in patients who have received multiple transfusions. Storage of cellular blood compounds may release cytokines which are responsible for this transfusion reaction. Pre-storage leukocyte depletion of RBCs and platelets by filtration may prevent this reaction. Occasionally, this transfusion reaction may be quite severe and needs to be distinguished from bacterial contamination, which is associated with rigors, higher fever and with other features of sepsis.

The transfusion should be discontinued and recipient blood as also that which has been transfused should be sent for culture.

Acute Hemolytic Reactions

Acute hemolytic reactions are almost always due to human error due to transfusion of incompatible blood. ABO incompatibilty is the most common, as anti-A, anti-B antibodies occur naturally. However, other antibodies due to prior sensitization can also cause acute hemolysis. Incompatible blood transfusions can be prevented by adhering to a strict protocol for blood collection, labeling, storage, release and the final checking of the correctness of the unit, prior to administration to the patient.

Hemolytic transfusion reactions may vary from the mild to the fulminant and fatal. Back pain, fever and chest tightness are the warning complaints in conscious patients. If the patient is undergoing surgery under general anesthesia, unexplained hypotension, tachycardia, fever and red scanty urine are observed. Recovery from anesthesia may be slow. High fever with chills, sometimes accompanied by seizures, may occur at this stage. There also may be generalized oozing from venepuncture sites due to an evolving DIC.

Acute hemolytic transfusion reactions often produce acute oliguric renal failure. Hemoglobinuria is present, and there is an increase of free hemoglobin in the blood. Cardiovascular collapse and DIC are important complications, which are due to immune complex deposition and stimulation of the coagulation cascade, resulting in a consumption coagulopathy. In severe cases, perfusion to vital organ systems

is grossly impaired, leading to tissue hypoxia and damage. The degree of damage is dose-related. For this reason, even mild febrile reactions occurring in a patient receiving a transfusion should prompt a stopping of the transfusion, checking the label and group of the blood product being used, and checking with the blood bank regarding the possibility of incompatibility. This is particularly important if the patient is being transfused for the first time, or has never exhibited transfusion reactions in the past.

Management of an acute severe hemolytic reaction requires critical care. Vital signs are monitored, and a volume load infused to maintain adequate blood pressure and renal perfusion. Furosemide 40–100 mg intravenously together with intravenous fluids and mannitol should be used to help to maintain a urine output of 100 mL/hour or more. Furosemide should be given in a continuous intravenous infusion at the rate of 20–40 mg/hour if the urine output falls. Renal function should be monitored, and baseline coagulation studies should be done and repeated at periodic intervals. If acute renal shutdown due to acute tubular necrosis occurs in spite of the above measures, treatment is as for acute renal failure. DIC may need to be treated by replacement of clotting factors and/or by infusion of cryoprecipitate. Hemodialysis may be necessary for renal support till such time as renal function returns to normal.

Delayed Hemolytic Reactions

These are mild and generally occur 1 week after transfusion. Initial crossmatching fails to detect antibodies to the donor red cell antigens. Prior sensitization by transfusion of RBC antigens not belonging to the ABO group results in a transient rise in antibodies. The titer of these antibodies wanes within a few weeks, and may not be detectable. A second transfusion with a repeat exposure to the red cell antigen provokes an anamnestic rise of the antibody to a degree sufficient to cause hemolysis.

Transmission of Infection[11]

The risk of transmitting infections through blood transfusions can never be entirely eliminated.

Bacterial contamination of RBCs and platelets during collection can have disastrous consequences. In tropical developing countries, donor blood could transmit malaria, typhoid, dengue or other infectious diseases, if the donor donates blood when infected.

Contamination with cold-loving organisms as for example, yersinia can occur. The CMV virus, other viruses, prion-causing Creutzfeldt-Jakob disease and rarely syphilis have been known to be transmitted through transfusions.

The major risk is with transmission of hepatitis B, C viruses and HIV virus I and II. However, by current technique of screening blood using polymerase chain reaction (PCR) test for hepatitis C and HIV ribonucleic acid (RNA), the estimated risk per unit of blood is as low as 1 in 2 million for HIV and hepatitis C.

Risk for viral transmission of hepatitis B is estimated 1 in 500,000. These are American figures. Risks for transmission of infection in poor developing countries must indeed be much higher.

Transfusion-related Graft versus Host Reaction

Though rare, this reaction can prove fatal. It occurs 2–30 days after transfusion and is characterized by fever, rash, diarrhea, increasing hepatic dysfunction and severe pancytopenia. This reaction occurs in patients with a marked defect in cellular immunity as is seen in lymphoproliferative disorders. Transfusions from relatives and HLA compatible donors can result in this dangerous reaction. It can be prevented by gamma radiation of cellular blood components. The reaction is due to donor lymphocytes that engraft and multiply in response to the host antigen.

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CHAPTER 59

Endocrine Dysfunction

ACUTE ADRENAL CRISIS

GENERAL CONSIDERATIONS

Acute adrenal crisis or adrenocortical insufficiency is due to a severe lack or deficiency of adrenocortical hormones. It is a critical illness requiring intensive care, and is quickly fatal unless promptly recognized and treated.[1] Early diagnosis is essential, but so protean are the manifestations that delay in diagnosis is common. An awareness of the background factors against which acute adrenal crisis suddenly unfolds should make one suspect the diagnosis. Suspecting adrenal crisis is, in fact, a major step towards arriving at the correct diagnosis.

Acute adrenal insufficiency is rather infrequently encountered in patients under critical care. It does, however, occur under the following situations—

- Following sudden withdrawal of corticosteroids in a patient whose own adrenal glands have been suppressed by prolonged administration of corticosteroids. If these patients undergo stress in the form of surgery or an acute infection, they require a larger dose of corticosteroids. Sudden withdrawal of the drug can precipitate an acute crisis, which, if not promptly recognized, can prove fatal. More often than not, the drug is not administered in the intensive care unit (ICU) because the physician is unaware that the patient was on a maintenance dose of corticosteroids.
- Acute stress in a patient with latent adrenocortical insufficiency—the stress may be in the form of prolonged anesthesia and major surgery, acute infection, trauma, and occasionally following a difficult, protracted delivery in females. Relative adrenocortical insufficiency has been shown to exist in critically ill patients with severe sepsis; cortisol levels may be normal, but do not rise appropriately after adrenocorticotropic hormone (ACTH) stimulation.[2,3]
- As a complication in a patient with overt chronic adrenocortical failure—this is not as uncommon as is believed to be. A frequent cause of chronic adrenocortical insufficiency, in our part of the world, is tuberculous destruction of both the adrenal glands. In the West, autoimmune disease destroying the adrenals is far more frequent.
- Acute bilateral destruction of the adrenal glands by hemorrhage[4]—this occurs after trauma and in fulminant infections (Waterhouse-Friderichsen syndrome). Meningococcal septicemia is an important cause of the Waterhouse-Friderichsen syndrome. Adrenal hemorrhage has also been reported in pneumococcal, staphylococcal and Haemophilus influenzae infections. Pseudomonas aeruginosa infection in children is also an important cause of sepsis producing adrenal hemorrhage. Other causes of bilateral adrenal hemorrhage include anticoagulant therapy, disseminated intravascular coagulopathy and rarely acute bilateral venous thrombosis causing hemorrhagic infarcts in patients with antiphospholipid antibody syndrome.
- Acute adrenal insufficiency following bilateral adrenalectomy or following removal of a unilateral adrenocortical tumor, which has suppressed the opposite gland, does not pose problems in diagnosis.
- Very rarely, shock, peripheral circulatory failure and a collapsed state are observed following hemorrhage into

Box 1: Important causes of adrenocortical insufficiency

- Withdrawal of steroids in patients receiving corticosteroids for a long time
- Infections—tuberculosis, fulminant sepsis due to Gram-positive or Gram-negative bacteria, fungal infections, cytomegalovirus infection, HIV
- Adrenal hemorrhage—fulminant infection or use of anticoagulants, DIC, antiphospholipid antibody syndrome
- Autoimmune destruction
- Bilateral metastatic adrenal disease
- Medications—megestrol acetate (decreased secretion of ACTH); ketoconazole (decreased cortical synthesis); rifampin, phenytoin (increased metabolism of cortisol)
- Hypothalamic and pituitary disorders (secondary adrenocortical insufficiency)
- Relative adrenal insufficiency in some patients with severe sepsis

Abbreviations: HIV, human immunodeficiency virus; DIC, disseminated intravascular coagulation; ACTH, adrenocorticotropic hormone.

the pituitary (pituitary apoplexy), which causes acute adrenocortical failure.

Important causes of adrenocortical insufficiency are given in Box 1.

CLINICAL FEATURES[1,5]

The clinical features are protean, and, at times, bizarre, so that diagnosis depends on a high index of suspicion.

The onset may be explosive, and, at times, is characterized by fever, confusion, and drowsiness graduating to severe mental obtundation and even coma. In some patients, the temperature is subnormal, and severe asthenia predominates, so that the patient is unable to even turn on his own in bed. Abdominal symptoms are very frequently present. Abdominal pain may be severe, and may mimic an acute abdomen. Nausea, vomiting and diarrhea are often observed, and confuse the clinical picture. However, the most striking feature in all patients is the rapid development of peripheral failure and shock, characterized by a rapid thready pulse and progressive hypotension. The shock resembles hypovolemic shock, but is not corrected by volume replacement or the use of inotropic support; quick improvement only follows after the use of adrenocortical steroids.

In the Waterhouse-Friderichsen syndrome, the explosive onset with high fever, headache, vomiting and prostration is accompanied by purpuric skin rashes. These rashes may be confluent producing large areas of hemorrhage. Respiratory distress, cyanosis and a quickly evolving irreversible state of shock are observed with death occurring within 24–48 hours.

LABORATORY INVESTIGATIONS

- A moderate degree of hyponatremia may be present; it may be associated with hyperkalemia. Hyponatremia is most often related to an associated mineralocorticoid deficiency. These patients, however, become hyponatremic even in the presence of a positive sodium balance. This indicates inability to excrete free water due to glucocorticoid insufficiency.
- Urea, creatinine and nonprotein nitrogen levels in the blood are raised due to prerenal factors.
- Hypoglycemia is often observed. Glucocorticoids play an important role in gluconeogenesis and counter the action of insulin.
- Blood cortisol levels are very low and do not show an adequate response to the ACTH stimulation test. The ACTH stimulation test is the definitive test for adrenal hypofunction. After administration of synthetic ACTH, an adequate adrenal response shows a 10 μg rise in cortisol level over baseline at 60 minutes, or a stimulated cortisol level greater than 20 μg/dL. Values below those stated above point to adrenal hypofunction. Cortisol values greater than 20 μg before or after ACTH stimulation are compatible with normal adrenal function. The interpretation of the ACTH stimulation test should, however, take into consideration the fact that cortisol is bound to corticosteroid-binding globulin and albumin and these are often reduced in critically ill patients.

  Primary adrenocortical insufficiency should be distinguished from secondary adrenal insufficiency. The aldosterone response to ACTH stimulation are impaired in primary adrenocortical insufficiency, but preserved in secondary adrenocortical insufficiency. Also, ACTH levels in blood are raised in primary adrenocortical insufficiency and below normal in secondary adrenocortical insufficiency. The clinical features of hyperpigmentation of the mucosa and skin and the presence of hyperkalemia are characteristics of primary adrenocortical insufficiency. They do not occur in secondary adrenocortical insufficiency.
- Adrenocortical insufficiency may be associated with hypothyroidism and other hormonal deficiencies. If clinical suspicion exists, relevant tests for other hormonal deficiencies should be done.
- In the Waterhouse-Friderichsen syndrome, blood cultures are generally positive. Organisms may be seen in petechial scrapings.

DIAGNOSIS[1,2,5]

The possibility of acute adrenocortical insufficiency should always be considered when faced with any acute illness in the ICU, which is characterized by protean manifestations and peripheral circulatory failure. The background against which acute adrenal insufficiency occurs, should always be kept in mind as it affords an invaluable clue to the diagnosis. Inexplicable shock occurring after a straightforward operation (e.g. appendicectomy or herniorrhaphy), or in a patient with an ordinary infection, should always suggest the possibility of acute adrenal crisis.

An important cause of hyperpyrexia with prostration and collapse is acute adrenocortical failure. In such cases, the diagnosis is often confused with an acute infection like malaria, pneumonia, sepsis or even meningitis. Quite often an acute infection precipitates adrenocortical failure, so that the confirmed presence of the former, in no way excludes the latter.

In patients, who are drowsy or mentally obtunded, the differential diagnosis of poisoning, cerebrovascular accidents or other causes of a semiconscious state should be considered.

The occurrence of acute abdominal pain and vomiting continues to fox the most experienced of clinicians. An earlier history of asthenia, hypotension, mucosal pigmentation, and pigmentation of the exposed parts, particularly the creases of the palms, and of the skin over the knuckles should suggest the diagnosis.

The diagnosis of an acute adrenal crisis requires a high index of suspicion and is necessarily clinical. In most ICUs in our country, the diagnosis cannot be immediately confirmed by objective laboratory tests. Treatment should be immediate and vigorous. If possible, a blood sample should be collected for cortisol assay and this can be repeated after 1 hour of ACTH stimulation. The patient, however, needs to be given a glucocorticoid without awaiting results. Dexamethasone 4 mg, intravenously given as a bolus dose, does not interfere with cortisol assays. Recovery of the patient following correct treatment is probably the most reliable objective pointer to a correct diagnosis.

TREATMENT[2,5]

Treatment should be prompt. If the ACTH stimulation test has been done, dexamethasone 4 mg intravenously is administered, without awaiting the results of the test.

Use of Glucocorticoids

Hydrocortisone hemisuccinate in a dose of 100–200 mg is given intravenously 6 hourly over the first 24 hours. The drug may be given either as a continuous intravenous infusion or as a bolus IV injection. The dose of intravenously administered hydrocortisone over the next 24 hours should also be 300–400 mg. By this time, recovery is apparent, so that from the third day onward, the dose is reduced by 25–50 mg/day, and within the next 8–10 days, the patient is on a maintenance dose of 100 mg hydrocortisone daily. Once the crisis is over, the patient is put on oral prednisolone + mineralocorticoid therapy (fludrocortisone 0.05–0.1 mg/day), and IV hydrocortisone is omitted. The above is a general outline of dosage requirements in patients in an acute crisis. The dosage may need to be modified according to the patient's response. As a general rule, adrenal insufficiency is one of those rare situations where it is safer to overtreat than to undertreat. A careful watch on the side effects of corticosteroid therapy must be maintained.

An acute crisis can be prevented, if patients with underlying adrenocortical insufficiency (on a maintenance dose of corticosteroids) are given larger doses during the stress of surgery or acute infection. Empiric recommendations are 25 mg/day of hydrocortisone for mild stress, 50–75 mg/day for 2–3 days for moderate stress and 100–150 mg/day for 2–3 days for severe stress. After recovery from stress, patients are placed on a maintenance dose of 15–30 mg/day.

Restoration of Fluid and Electrolyte Balance

Dehydration and salt depletion characterize an adrenal crisis, and it is important to quickly correct these abnormalities. During the first 24 hours, the usual requirement is at least 2 liters of normal saline. The administration of fluid and electrolytes should be monitored by clinical examination, by central venous pressure measurements and by estimation of serum electrolytes. Many patients, who have not been correctly diagnosed, or diagnosed late, are often already excessively volume loaded, in an attempt to correct shock and hypotension. Further volume loading in these patients is unnecessary and may precipitate acute pulmonary edema.

Serum potassium may fall during recovery from a crisis. This is particularly likely if large doses of glucocorticoids continue to be used; potassium replacement is necessary in these patients.

Vomiting is often present and precludes oral feeds in the first 24–48 hours. Nutrition is poor in many of these patients, and this should be carefully supplemented once oral feeds are tolerated.

Dextrose Infusion

Hypoglycemia, though generally not marked, needs to be countered by an IV infusion of dextrose. One liter of 10% dextrose is infused in the first 24 hours, followed by 500 mL of the same solution in the next 24 hours. By this time, the patient is generally out of the crisis and can take glucose orally in fruit juice or other liquids.

Treatment of Precipitating Factors

It is important to identify and treat these factors. Infection, in particular, is the most important precipitating cause and needs the use of appropriate antibiotics. Fulminant infections causing bilateral adrenal hemorrhage are often fatal. They require the use of antibiotics in massive doses, chosen according to the nature of the infection, and expert overall critical care. A few patients with adrenocortical insufficiency also have other endocrinopathies, which should be identified and treated. Patients suffering from combined adrenocortical and thyroid deficiency should first receive corticosteroids to correct the cortisol deficiency and then treated with eltroxin to correct hypothyroidism. Initial correction of hypothyroidism without correcting adrenocortical insufficiency can precipitate a worsening acute adrenal crisis. The treatment of an acute adrenal crisis is summarized in Box 2.

Box2: Treatment of acute adrenal crisis

- Intravenous hydrocortisone 100 mg 6 hourly in the first 24–48 hours; this is gradually reduced over the next 5 days. Use oral prednisolone or oral hydrocortisone + a mineralocorticoid subsequently
- Restore fluid and electrolyte balance—
  - Two liters of N saline in the first 24 hours—monitor volume infusions clinically and with central venous pressure (CVP), particularly in patients who have received large volume loads prior to arriving at the correct diagnosis
  - Correct hypokalemia during recovery
- Intravenous dextrose infusions to counter hypoglycemia. One liter of 5–10% dextrose is generally necessary over 24 hours
- Diagnose and treat precipitating factors—chiefly infection

CRITICAL ILLNESS-RELATED CORTICOSTEROID INSUFFICIENCY[5]

There could be a relative deficiency of cortisol in patients with severe sepsis, septic shock and acute respiratory distress syndrome (ARDS). Recommendations for the use of corticosteroids cannot be made with definite certainty. The subject has been discussed in the Chapters Intra-Abdominal Sepsis and Acute Lung Injury and Acute Respiratory Distress Syndrome. The options on whether to use or not use steroids in suspected hypoadrenal crisis in critically ill patients are still open. If IV cosyntropin (synthetic ACTH) results in an inadequate cortisol response, hydrocortisone is indicated.

COMPLICATIONS DURING TREATMENT OF AN ADRENAL CRISIS

- Overhydration occurs when a massive volume load has been administered prior to establishing a correct diagnosis. This is generally done as a measure of desperation to reverse shock. Once a diagnosis is made in these patients, the combination of further infusions of N-saline with large doses of IV hydrocortisone can produce cerebral edema or pulmonary edema. Cerebral edema may result in seizures and unconsciousness; pulmonary edema may be fatal.
- Severe hypokalemia with increasing asthenia, flaccid muscle weakness of the limbs, abdominal distension and arrhythmias may complicate recovery from a crisis. Serum potassium levels, as explained earlier, should be carefully monitored, and, if present, hypokalemia should be corrected by administration of potassium.
- Hyperpyrexia may occur as part of an acute adrenal crisis. Rarely, it is observed during recovery following the use of IV corticosteroids and saline infusions.
- Important and frequently encountered side-effects of corticosteroid therapy include acute gastrointestinal bleeding and acute psychotic reactions.

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THYROID DYSFUNCTION AND EMERGENCIES MERITING CRITICAL CARE

Life-threatening problems[1] in thyroid disease requiring critical care include the following—

1. Thyroid storm or crisis occurring in a patient with a hyperfunctioning thyroid gland.
2. Sudden atrial fibrillation with a very fast uncontrollable ventricular rate leading to acute congestive failure, occurring as a complication of hyperthyroidism.
3. Myxedema coma due to a markedly poor function of the thyroid gland.
4. Hemorrhage into one or more nodules of a nodular goiter can lead to acute compression of the trachea in the neck, and hemorrhage into a substernal goiter can lead to acute mediastinal compression, necessitating urgent surgical intervention.

The first three conditions requiring critical care are discussed in this chapter. This is followed by a brief description of the euthyroid sick syndrome, a commonly encountered abnormality in a critical care setting.

THYROID CRISIS (THYROID STORM)[1,2]

A thyroid crisis or storm is a life-threatening metabolic storm resulting from a marked increase in free thyroxine (T_4) circulating in the blood. The thyroid gland runs amuck, berserk with marked increase in its activity and its hormonal output, thereby producing an excessive metabolic rate, which the body cells cannot withstand.

The fulminant forms of thyroid crisis, which can kill a patient within 24–48 hours, usually occur following surgery on an uncontrolled hyperfunctioning thyroid gland. These are now fortunately rare since surgery on a hyperfunctioning thyroid gland is never done without prior control of thyroid activity by proper medical treatment. In present days, a crisis is most often precipitated in a patient with hyperthyroidism by an acute infection or by the stress of major surgery. Other precipitating causes include trauma, severe psychological stress, diabetic ketoacidosis, treatment of uncontrolled hyperthyroidism with radioactive iodine, or withdrawal of drugs given to control hyperthyroidism. The patient may be admitted to the ICU for a thyroid crisis. At times a patient with underlying undetected hyperthyroidism is admitted for another life-threatening problem. A crisis in this situation is precipitated by some of the factors outlined above following admission to the unit. In these critically ill patients, even if the degree of hyperthyroidism does not amount to an acute crisis, it is sufficient to add significantly to the gravity of the clinical situation. Thyrotoxicosis can also be induced in critically ill patients following the use of iodine-rich drugs—amiodarone, povidone-iodine and radiographic contrast agents.[3,4]

Box 3 lists the important precipitating factors of an acute thyroid crisis.

Box 3: Important precipitating factors of acute thyroid crisis

- Acute infection
- Stress of trauma/major surgery
- Severe psychological stress
- Diabetic ketoacidosis
- Sudden withdrawal of drugs used to control hyperthyroidism
- Treatment of uncontrolled hyperthyroidism with radioactive iodine
- Following surgery on uncontrolled hyperfunctioning thyroid gland

Clinical Features

The clinical picture is characterized by a marked increase in all the symptoms and signs encountered in thyrotoxicosis. Fever, marked restlessness, irritability and tachycardia that may be as high as 160–200 min, dominate the picture. In hot climes, hyperpyrexia with temperature greater than or equal to 106°F may be noted. Atrial fibrillation with a fast ventricular rate as also other forms of supraventricular tachycardia are common. The circulation is hyperdynamic with tachycardia, warm peripheries, bounding high volume pulse and a high pulse pressure due to elevation in the systolic reading and lowering of the diastolic pressure reading. The presence of diffuse enlargement of the thyroid gland (with an auscultatory bruit over it), exophthalmos, lid lag are classic features of Graves' disease. One or more nodules in the thyroid may be palpable in a toxic nodular goiter.

Abdominal pain and vomiting may occasionally usher a crisis. In these patients, or even otherwise, diarrhea may be a presenting feature. Patients in a crisis do not eat well and may have anorexia. This should never negate the diagnosis of severe hyperthyroidism.

In elderly patients, a thyroid crisis may just present with marked apathy, extreme weakness and unexplained fever. Diarrhea is frequent and paroxysmal disturbances in cardiac rhythm are common. Death in a thyroid crisis may be due to hyperpyrexia or cardiac failure.

Diagnosis

A thyroid crisis precipitated by surgery is often missed for an acute postoperative infection or a transfusion reaction. With a known background history of hyperthyroidism, the diagnosis of a sudden spurt in hyperthyroid activity should always be given prior consideration in a patient who develops a febrile illness, or does poorly following surgery.

Patients first seen in a crisis, who are unaware of a hyperthyroid background, may pose difficulties in diagnosis. Common errors are to mistake thyroid crisis for sepsis, heat stroke, an acute gastrointestinal infection or ischemic heart disease.

In patients presenting with hyperpyrexia, delirium and tachycardia, the differential diagnosis should include sepsis, malignant hyperthermia, neuroleptic malignant syndrome and acute mania with catatonia. The first three of these conditions could be associated with or indeed precipitate a thyroid storm.

A careful clinical examination for tell-tale features of hyperthyroidism is invariably rewarding. Atrial fibrillation with an uncontrolled fast ventricular rate, which is not slowed with digitalis, should always arouse suspicion. An extremely valuable sign that helps in the diagnosis of a thyroid crisis is the presence of an enlarged thyroid gland or the presence of one or more palpable nodules in the thyroid gland. This enlargement is often not obvious and requires careful clinical palpation. Clinical examination should also be directed towards determining the precipitating cause of a thyroid crisis.

Laboratory Investigations

The triiodothyronine (T_3) and T_4 concentrations are high, but these are not necessarily greater in a thyroid storm than in the usual thyrotoxic state. The thyroid-stimulating hormone (TSH) is low. In critically ill patients, free T_4 and TSH should be measured. *Clinical hyperthyroidism results in an increased free T_4 and a suppression of TSH to less than 0.01 μU/L.* A TSH within normal range should exclude hyperthyroidism. However, TSH may occasionally be low in about 10% patients with nonthyroid critical illness, in patients on dopamine and in patients on a high dose of glucocorticoids. Hence, though an (unsuppressed) normal TSH excludes hyperthyroidism a low TSH does not always establish the diagnosis. A normal free T_4 with a reduced TSH should prompt the intensivist to search other causes (stated above) for a low TSH. It should be noted that heparin therapy can artificially increase plasma free T_4; in heparin-treated patient, the total T_4 should be measured.

There are no other laboratory abnormalities characteristic of a thyroid storm. Hypercalcemia, hyperglycemia and a rise in alkaline phosphatase may be noted. Hyperglycemia is due to gluconeogenesis. There is decreased glucagon suppression and impaired insulin response to hyperglycemia. Electrocardiography (ECG) may show atrial fibrillation or atrial flutter with a fast ventricular rate.

Management: Prevention

Surgery on a hyperthyroid gland should never be performed until the thyrotoxic state is controlled with neomercazole or by the thiouracil group of drugs. Neomercazole (carbimazole) is stopped 8 days before planned surgery, and Lugol's iodine substituted during these 8 days in a dose of 0.1–0.3 mL thrice daily. Following the above precautions, thyroid crisis following surgery on a hyperthyroid gland is extremely rare. The awareness of the fact that all stressful situations (physical or mental) in hyperthyroid patients are potential triggering factors for a thyroid crisis, goes a long way in the prevention of this serious problem.

Treatment of Thyroid Crisis[1,2,5]

Control of the Hyperthyroid State

Use of thiouracils, carbimazole and methimazole Propylthiouracil is the drug of choice. It is given in a loading dose of 600 mg, followed by 250 mg 6 hourly. The drug is not easily available in India. Carbimazole or methimazole is available and the drug is given in a dose of 20 mg three to four times a day. All three drugs have a rapid onset of action and act by inhibiting iodide oxidation and organification by thyroid peroxidase. Propylthiouracil has the additional advantage of being able, to an extent, to inhibit the peripheral conversion of T_4 into T_3. Common side effects of antithyroid drugs are rash, urticaria, arthralgia and fever. Rarely agranulocytosis and hepatic toxicity may be observed.

Use of iodine Intravenous sodium iodide is the quickest method to control thyroid activity in a thyroid storm. Iodine acts by blocking the synthesis and release of thyroid hormones, but is safe to administer only after organification of iodine is arrested by propylthiouracil. It should, therefore, be given 1–2 hours after the first dose of propylthiouracil or carbimazole or methimazole.

Sodium iodide is given in a dose of 1 g in 500 mL dextrose over 8–12 hours. A total dose as high as 3 g may be given over the first 24 hours.

A maintenance dose of 0.5 g may then be given daily for the next 2 days. Lugol's iodine may be given orally if sodium iodide is not available for IV use. The dose is 3–5 drops (6 mg/drop) thrice daily. Potassium iodide can substitute for Lugol's iodine, and is given in a dose of 200 mg 12 hourly. Iodine is preferably stopped after 5–7 days.

Studies have shown that ipodate sodium (an iodine-containing radiocontrast agent), when given orally, has an extremely rapid onset of action, resulting in a lowering of T_3 levels within 6 hours with normal T_3 levels within 24–48 hours. The dosage is 500 mg four times a day. We have no experience with its use, but this drug, when available, has replaced Lugol's iodine and potassium iodide in the treatment of severe hyperthyroidism. Ipodate sodium should be given 1–2 hours after the first dose of propylthiouracil or carbimazole or methimazole.

Use of beta-blockers Beta-blockers are the drugs that best counter the catecholamine-dependent symptoms and signs of an acute thyroid crisis. They play a vital role in treatment as they control both the psychomotor and cardiovascular manifestations that typify a thyroid storm. Beta-blockers reduce the heart rate in patients with marked sinus tachycardia, reduce the fast ventricular rate in patients with atrial fibrillation and often succeed in restoring sinus

rhythm in patients with atrial fibrillation and supraventricular tachycardias.

Propranolol is given in a dose of 40–60 mg orally three to four times a day. Propranolol has the advantage of decreasing the conversion of T_4 into T_3. Though the drug can be given very slowly intravenously in a dose of 0.5 mg to start with, the IV use is best avoided because of the reported experience of sudden bradycardia and arrest after IV use of the drug.

A quicker beta-blocade is provided by esmolol 500 μg/kg IV followed by 50 μg/kg per minute IV. Metoprolol can also be used as an alternative to esmolol—5 mg IV repeated every 5–10 minutes to a maximum of a total dose of 15 mg IV. The oral dose of metoprolol is 50–100 mg twice daily. Atenolol can be used likewise in the same dose.

Though beta-blockers are very useful drugs (particularly in the presence of tachyarrhythmias), they should be used with great caution in patients who have congestive cardiac failure. Marked hypotension and cardiac arrest may occur following their use in these patients.

Use of adrenocortical hormones Glucocorticoids are useful to prevent adrenocortical insufficiency. The rate of utilization of adrenocortical hormones is excessive in a thyroid crisis, and it is possible that some patients may have a relative conditioned deficiency of these hormones. Hydrocortisone is given routinely in a dose of 100 mg intravenously 8 hourly till the crisis is controlled. Besides offering adrenocortical support, glucocorticosteroids are of benefit because they inhibit peripheral conversion of T_4 to T_3.

Control of Atrial Fibrillation

Atrial fibrillation with a fast ventricular rate generally does not respond satisfactorily to digitalis. Propranolol given in the manner described above is the drug of choice. Metoprolol is longer acting and may also be given intravenously in an initial dose of 5 mg given at a rate of 1–2 mg/minute, to a total dose of 10–15 mg.

In an acute hemodynamic crisis with a barely recordable blood pressure and the presence of features of cardiogenic shock, a synchronized direct current (DC) shock should be promptly administered. It generally restores sinus rhythm. Once this is achieved, a beta-blocker is used as mentioned earlier.

Digoxin (even though the response is generally unsatisfactory) and diuretics may also be used in atrial fibrillation with congestive cardiac failure. If atrial fibrillation persists, anticoagulants should be given to prevent embolic episodes.

Treatment of Hyperpyrexia

Symptomatic treatment of hyperpyrexia is necessary in a few patients; else death can result before more definitive therapy can take effect.

Control of Restlessness, Excitability and Irritability

Restlessness is controlled by the use of phenobarbitone sodium 60 mg intramuscularly or chlorpromazine hydrochloride 25–50 mg intramuscularly or the use of 5 mg diazepam IV. This can be repeated as and when necessary.

Maintenance of Fluid and Electrolyte Balance

Patients suffering a thyroid storm sweat profusely. This is even more marked in hot tropical climes. A tremendous loss of water, sodium and chloride occurs. Potassium loss is also marked because of diarrhea and a poor intake. A fluid intake well over 3 liters and, at times, exceeding 4 liters, is necessary. It is, however, worth recording that pulmonary edema is an important complication of thyroid crisis. A close monitoring of the cardiovascular status, renal function and urine output is necessary. Fluid and electrolyte replacement should be based on clinical considerations and on serum electrolyte estimations.

Since hepatic glycogen is used up quickly in a thyroid crisis, fluid replacement should include at least 1 liter of 10% dextrose. The hypermetabolic state in a thyroid crisis places an excessive demand on nutrients and vitamins necessary for proper functioning of different tissues in the body. The demand particularly for thiamine may be great. In poorly nourished individuals so commonly encountered in the tropics, an acute thiamine deficiency may arise, particularly if large quantities of dextrose are given intravenously and an adequate dose of thiamine (200–500 mg) is not supplied.

Use of Oxygen

The demand and consumption of oxygen are excessively increased in the hypermetabolic state that characterizes a crisis. The patient is given oxygen at a flow rate of 6–8 L/minute.

Note It is important to treat the underlying illness that could have triggered a thyroid storm or crisis.

The management of an acute thyroid crisis is summarized in Box 4.

HYPERTHYROIDISM CONTRIBUTING TO THE MORBIDITY OF OTHER CRITICAL ILLNESSES IN THE ICU

The commonest cause of hyperthyroidism is Graves' disease which in a florid state is easily diagnosed but may be missed in early or an evolving state. Other causes include a toxic nodular goiter and a thyroid adenoma. The above conditions are associated with an increased iodine-131 uptake by the gland. Hyperthyroidism can also be induced by the use of amiodarone, iodine-containing contrast media, or can result from acute or subacute thyroiditis. Rarely, hyperthyroidism may be due to the purposeful ingestion of thyroid hormone—factitious hyperthyroidism. All these conditions are associated with a decreased iodine-131 uptake by the gland.

Undetected hyperthyroidism in patients admitted to the ICU for other critical illnesses can pose diagnostic problems, and can add to the morbidity of the critical illness. The stress of a critical illness often increases the degree of hyperthyroidism in a patient, so that mild or latent

Box 4: Management of acute thyroid crisis

- Control of hyperthyroid state
- Propylthiouracil 250 mg 6 hourly or carbimazole 30 mg 6 hourly
- One gram sodium iodide in 500 mL dextrose, given as an IV infusion, followed by a maintenance dose of 0.5 g daily for the next 2 days. Alternatively, 3–5 drops (6 mg/drop) of Lugol's iodine are given orally thrice daily. Start iodine 1–2 hours after first dose of propylthiouracil or carbimazole
- Propranolol 40 mg qds orally or esmolol in an IV infusion (see text) or metoprolol 5 mg IV repeated every 5–10 minutes for a total of 15 mg
- Hydrocortisone 100 mg is given IV 8 hourly or dexamethasone 2 mg IV qds
- Control of atrial fibrillation and other tachyrhythms—
  - Metoprolol 5 mg IV (at the rate of 1–2 mg/min) up to a total dose of 10–15 mg
  - Propranolol 40–60 mg tds
  - Synchronized DC shock given in acute hemodynamic crisis
- Symptomatic treatment of hyperpyrexia
- Control of restlessness and irritability with phenobarbitone sodium 60 mg IM or chlorpromazine 25–50 mg IM or diazepam 5–10 mg IV repeated as and when required
- Maintenance of fluid and electrolyte balance—
  - Three to four liters of fluid infused over 24 hours after monitoring the patient's cardiovascular status and urine output
  - Correct hyponatremia, hypokalemia
  - Intravenous dextrose—at least 1 liter of 10% dextrose required in 24 hours
  - Administer 200–500 mg thiamine, particularly in poorly nourished patients
- Administer oxygen at a flow rate of 6–8 L/min
- Identify and treat precipitating factor—in particular, underlying sepsis

hyperthyroidism now becomes clearly manifest. The features of such coexisting hyperthyroidism often merge and may well be indistinguishable from the features of the critical illness for which the patient is admitted.

Hyperthyroid activity in these patients generally takes the following forms—

- Pyrexia of unknown origin, which fails to respond to antibiotics given because of a mistaken diagnosis of infection.
- An unstable hyperdynamic circulation which is generally attributed to the critical illness for which the patient was admitted, or to complicating sepsis.
- Rhythm disturbances with or without congestive cardiac failure, or the evolution and persistence of congestive cardiac failure with a fast ventricular rate.

The following points help in correct diagnosis—

- The possibility of hyperthyroidism should always be considered at any age when a patient develops atrial fibrillation, a fast ventricular rate and congestive cardiac failure, which does not promptly respond to digitalis. Most such patients are past 40 years in age and may complain of cardiac pain due to relative coronary insufficiency produced by a very rapid ventricular rate. This often makes the unwary fall into the trap of diagnosing ischemic heart disease causing atrial fibrillation and congestive heat failure. Even if the patient has proven ischemic heart disease, as viewed from the past history and ECG recordings, this does not always exclude a coexistent hyperthyroid state.
- Paroxysmal atrial fibrillation, or any form of paroxysmal supraventricular tachycardia in a patient admitted to the ICU for a serious illness, should suggest the possibility of a coexisting hyperthyroid state.
- Hyperthyroidism should always enter into the differential diagnosis of congestive heart failure of undetermined etiology. A careful examination may reward the clinician with a few tell-tale signs, as, for example, the presence of a slight stare, a lid lag, a warm moist skin and an enlarged thyroid gland.

Raised free T_4 levels with a low TSH level prove the diagnosis of a hyperthyroid state in these patients.

The importance of a correct diagnosis is obvious. Manifestations of excessive thyroid activity can only be controlled by the specific measures stated earlier. They remain uncontrolled with conventional therapy used for atrial fibrillation or for congestive heart failure. It is important to control coexisting hyperthyroidism in critically ill patients. Control reduces the metabolic demands of the critical illness and should improve the chances of recovery.

MYXEDEMA COMA[6-8]

Myxedema coma is invariably the culmination of long-standing hypothyroidism. It may occur as the terminal event in the natural history of severe myxedema. It may however also be precipitated by exposure to cold, by infection and by the unwise use of sedatives to which patients with myxedema are extremely susceptible. Other precipitating factors include trauma, surgery, stroke, hypovolemia from any cause and congestive heart failure. Box 5 lists the important precipitating factors of myxedema coma.

Diagnostic Clinical Features

The onset is gradual particularly when myxedema coma is the terminal event of long-standing progressive hypothyroidism. It may be fairly abrupt if the problem is triggered by the precipitating factors listed above. The hallmark of myxedema coma is hypothermia—the rectal temperature being often less than 80°F. This is missed as it will not be recorded by a clinical thermometer; the degree of hypothermia can be ascertained with a chemical thermometer.

Box 5: Important precipitating factors of myxedema coma

- Infection
- Exposure to cold
- Injudicious use of sedatives and narcotics
- Surgery/Trauma
- Cerebrovascular accident
- Hypovolemia due to any cause
- Congestive heart failure

The cardiovascular system on examination shows marked bradycardia. The stroke volume and cardiac output are decreased; there is an increased peripheral vascular resistance with decreased blood volume and diminished blood flow to vital organs. The heart size is often enlarged; pericardial effusion is frequently observed. Signs of congestive heart failure—engorged neck veins, enlarged liver and pitting edema are often present. The blood pressure to start with may be noncontributory in the diagnosis. Terminally hypotension is invariably observed. There may be a rise in the creatine kinase (CK) and lactic acid dehydrogenase (LDH) enzymes, so that a diagnosis of myocardial infarction can be wrongly made. The ECG shows bradycardia and low voltage; conduction defects may occur in the sinoatrial (SA) node, atrioventricular (AV) node and in the bundle branches of His.

The respiratory system shows important changes. Hypoventilation with resulting hypoxia and hypercapnia are invariably present. There appears to be a decreased response to hypercapnia, so that uncontrolled oxygen therapy can complicate the picture by inducing hypercapnic narcosis and worsening the obtunded state. There are probably a number of causes for hypoventilation in myxedema coma. The most important reason is, in all probability, a diminished central respiratory drive, followed by poor muscle power, poor tone and poor contraction of the respiratory muscles. Contributory causes may be extreme obesity and obstruction to the upper airways due to macroglossia and to edema of the oropharynx. Marked sensitivity to the effects of sedatives and tranquilizers, narcotics and anesthetic agents can trigger both coma and hypoventilation in patients with myxedema.

The other tell-tale features are all there for those who have eyes to see; it is astonishing how these features are explained away! The dry, cool, puffy skin, the myxedematous facies, the constant drowsiness and confusion that precede coma, the loss of scalp and body hair (which includes the axillary hair), the macroglossia and delayed relaxation of the ankle reflex are all present.

Constipation is a nonspecific symptom but is almost always present. Ascites is uncommon, but, if present, may lead the unwary to a wrong diagnosis. Gastric atony and ileus involving both the small and large bowel are frequently observed. Urinary retention is common because of atony of the bladder.

A normocytic, normochromic anemia is present and the white blood cell count may be decreased. Inability to raise the core temperature or to generate a leukocytosis in response to infection renders the diagnosis of a complicating infection doubly difficult.

Box 6: Clinical features and laboratory abnormalities in patients with myxedema coma

- Hypothermia (except in the presence of infection)
- Clinical features of severe myxedema—
  - Dry, cool and puffy skin
  - Typical myxedematous facies
  - Loss of scalp and body hair
  - Drowsiness/mental obtundation preceding coma
  - Macroglossia
  - Delayed ankle reflexes
  - Atonic GI tract; atonic bladder
  - Marked bradycardia; ECG changes
  - Pleural, pericardial, peritoneal effusions
- Hypoventilation; hypercapnic respiratory failure
- Hypotension in terminal stages
- Laboratory abnormalities—
  - Normocytic, normochromic anemia, decreased WBC count
  - Hyponatremia, hypoglycemia, elevated levels of CK, LDH
  - T_3, T_4 levels decreased; TSH increased
  - Arterial blood gas (ABG)—PaO_2 decreased; $PaCO_2$ increased
- Radiological abnormalities—
  - Chest X-ray—cardiomegaly, pericardial effusion
  - Ultrasound of the abdomen—ascites may be present
- Hemodynamic parameters—
  - Decreased stroke volume and cardiac output
  - Increased peripheral vascular resistance
  - Decreased blood flow to vital organs

The clinical diagnosis of myxedema coma should be proved by low T_3, low T_4, and high TSH values. These values, however, need to be no different from those observed in a patient with obvious myxedema.

The basic features necessary for a clinical diagnosis and a summary of laboratory changes in patients with myxedema coma are summarized in Box 6.

Treatment[9-11]

The principles of treatment of myxedema coma are—

- ❑ Quick replacement of thyroid hormone.
- ❑ Use of adrenocortical steroids.
- ❑ Respiratory and cardiovascular support.
- ❑ Treatment of infection, a common precipitating factor.
- ❑ Countering hypothermia.
- ❑ Correction of hyponatremia.
- ❑ Overall critical care.
- ❑ Avoidance of all sedatives, hypnotics and narcotics.

Rapid Replacement of Thyroid Hormone

Use of L-T_3 sodium This is a rapid acting hormone whose main use is in severe myxedema or myxedema coma. T_4 given

orally acts far too slowly and, by the time the drug takes effect, the patient may succumb. The recommended dose of T_3 is 10 μg every 4–6 hours; this can be given intravenously or by nasogastric tube till clear improvement is observed. The IV preparation is not easy to come by, but if available, is to be preferred as absorption of both T_3 and T_4 from the gut is erratic and unpredictable. If the IV preparation is not available, oral T_3 is preferred to oral T_4, as the former is quicker acting. If oral T_3 is also unavailable, then one has to rest satisfied with the oral use of T_4. In Western countries, an IV T_4 preparation is available. The dose for myxedema coma is 500 μg as an IV bolus dose, followed by 50–100 μg daily. The dosage of the replacement hormones may need modification if anginal pains are frequent. Isosorbide dinitrate 10 mg thrice daily can be used if anginal pain occurs. After recovery, the patient is kept on a maintenance dose of either T_3 or T_4.

Use of Adrenocortical Steroids

There is a possibility that patients with severe myxedema have a poor adrenocortical reserve. What is more, it is difficult in an emergency situation to distinguish hypopituitary coma from a myxedema coma. To use thyroid hormone as the sole replacement hormone in a pituitary coma would provoke disaster, as the thyroid hormones would increase the metabolic rate and precipitate a severe adrenal crisis in such a patient. Hydrocortisone in a dose of 100 mg is therefore given intravenously every 8 hours.

Respiratory and Cardiovascular Support

Hypoventilation with hypercapnic respiratory failure needs to be treated by noninvasive ventilator support or by endotracheal intubation and mechanical ventilator support if the respiratory drive is very poor. This may need to be continued for 10–15 days. The airway must be kept patent, particularly, if the patient lacks the strength to cough, or is mentally obtunded with a poor cough reflex.

Hypotension needs to be countered by a volume load, provided there is no pulmonary edema. Inotropic support with dopamine should preferably not exceed 5–7 μg/kg per minute, as these patients are invariably severely vasoconstricted. Further vasoconstriction can jeopardize tissue perfusion.

Treatment of Infection

Infection is a common precipitating cause, and may not be clinically evident because of hypothermia, and the frequent absence of leukocytosis. Infection should be countered by the use of appropriate antibiotics. Terminal bronchopneumonia is common in such patients.

Raising the Body Temperature

Marked hypothermia may have to be corrected as an emergency measure. The body temperature should be raised very gradually; whenever possible, electric blankets or a heat cradle should be used. Sudden rewarming can cause peripheral vasodilatation and a crash in the already low arterial blood pressure. Ultimately, only a rise in the metabolic rate produced by the thyroid hormones can result in a sustained elevation of body temperature.

Correcting Hyponatremia

Myxedema coma is often accompanied by severe hyponatremia. Fluids should be restricted, and when necessary, a titrated volume of 3% saline is administrated.

Overall Critical Care

This is of great importance. Hyponatremia is often present and needs to be corrected. Hypertonic saline is avoided except under exceptional circumstances. Support to various other organ systems is often necessary. Patients in myxedema coma are often very poorly responsive to inotropes and vasopressors.

EUTHYROID SICK SYNDROME (SICK THYROID SYNDROME)

Thyroid function changes rapidly in critically ill patients. A number of these patients have the euthyroid sick syndrome. This syndrome is characterized by a low serum T_3 and T_4, and an increase in the L-reverse triiodothyroxine (rT_3).[12,13] The free fractions of T_3 and T_4 remain normal. This biochemical abnormality is due to inhibition of thyroid hormone binding to protein, and to diminished 5'-deiodinase activity. In healthy individuals, this enzyme catalyzes T_4 into the usual active T_3 in organs and tissues. On the other hand, the enzyme 5-deiodinase acts on T_4 and converts it to rT_3. 5-deiodinase, unlike 5'-deiodinase, is not affected by a critical illness. Therefore, T_3 levels are low, and rT_3 levels are increased in a critical illness. These patients are clinically euthyroid and have normal TSH levels.

The euthyroid sick syndrome is an adaptive phenomenon to a serious illness. The low T_3 levels limit oxygen utilization and reduce tissue breakdown. Administration of thyroid hormone is not indicated in these patients, and may harm as it promotes a negative nitrogen balance. In an ICU setting, it becomes important to distinguish the euthyroid sick syndrome, which does not require thyroid replacement therapy from true hypothyroidism. The serum TSH is usually normal in the euthyroid sick syndrome patients and high in true hypothyroidism. In critical illnesses, in which hypothyroidism is coexistent, TSH values are, however, not always reliable, as these values are not consistently elevated. A reliable method of estimating thyroid function in a critical illness is to estimate the free T_4 levels (normal in the euthyroid sick syndrome, and low in true hypothyroidism), or to perform the thyrotropin-releasing hormone (TRH) test. The free T_4 index can be estimated directly by the equilibrium dialysis method or is computed approximately by multiplying the T_4 concentration by the T_3 resin uptake. The TRH test is performed at the bedside by administering 250–500 μg of TRH intravenously. TSH levels are measured after 30 minutes. The patient with an euthyroid sick syndrome has a two to three times increase in the TSH after TRH test. A hypothyroid patient

has a rise of six to eight times in the TSH concentration after a TRH test.

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CHAPTER 60

Diabetes Mellitus

GENERAL CONSIDERATIONS

Patients with diabetes mellitus in the intensive care unit (ICU) generally present with the following problems—

- Complications of poorly controlled disease—particularly, diabetic ketoacidosis (DKA) and coma, and hyperosmolar nonketotic diabetic coma. The latter entity is also called, and synonymous with, hyperglycemic nonketotic hyperosmolar (HNHS) diabetic syndrome.
- Hypoglycemia induced by insulin or by an overdose of antidiabetic oral medications.
- One or more organ dysfunction associated with, or directly related to, poor control of diabetes.
- An unstable blood sugar with swings between hypoglycemia and hyperglycemia, induced by the stress of an unrelated critical illness.

The present section deals with DKA and coma, and with hyperosmolar nonketotic diabetic coma, both serious life-threatening metabolic disturbances associated with diabetes mellitus.

Diabetic Ketoacidosis and Coma[1,2]

Diabetic ketoacidosis is a serious metabolic disorder characterized by well-marked hyperglycemia [blood glucose >13.8 mmoL/L (250 mg/dL)], ketosis, metabolic acidosis and severe volume depletion with consequent dehydration.

Diabetic ketoacidosis chiefly occurs in insulin-dependent diabetics and its main cause is a severe lack or deficiency of insulin. It can, however, also occur, though less frequently in non-insulin (type 2) diabetes.

Failure to take insulin, or to meet the increased need for insulin during the acute stress of infection, illness or surgery, is the commonest cause of DKA. It is a common fallacy among insulin-dependent diabetics, that if they do not eat, they should not take insulin. This only serves to worsen the diabetic state, and increase the ketosis, which in turn, causes more nausea and vomiting.

Diabetic ketoacidosis is sometimes observed in a newly diagnosed insulin-dependent diabetic, the features of ketosis often drawing attention to the underlying diabetic state.

Dietary indiscretions with overindulgence in food are also observed to be a cause of DKA. Other precipitating factors include infections such as pneumonia, urinary infection, acute myocardial infarction and pancreatitis. Any condition causing high fever in an insulin-dependent diabetic can occasionally trigger DKA, if attention is not paid to the increasing requirements. The use of corticosteroids, catecholamines, inotropes and diuretics in insulin-dependent diabetics can result in a worsening diabetic state culminating in DKA.

There are many factors in an ICU setting that could potentially worsen diabetes and induce DKA. These include sepsis, use of parenteral nutrition involving a high carbohydrate intake and use of catecholamines. Even so, it is uncommon for severe DKA to develop de novo in the ICU, presumably because of increased vigilance that operates in the ICU setting.

Severe DKA is the forerunner of diabetic coma. A conscious diabetic with severe ketoacidosis should therefore be regarded and treated with the same urgency as one in diabetic coma. The dividing line between precoma and coma is thin and tenuous. Thus, a few patients remain conscious in spite of severe ketoacidosis till just some hours before death while others with the same degree of ketoacidosis lapse quickly into coma, which may be prolonged for 24–72 hours.

Box 1: Factors precipitating diabetic ketoacidosis

- Noncompliance with insulin therapy
- Newly diagnosed severe insulin-dependent diabetes
- Overindulgence in food
- Postsurgery
- Acute infections; acute febrile illness of any etiology
- Acute myocardial infarction
- Acute pancreatitis
- Use of glucocorticoids, catecholamines and diuretics
- Severe emotional, mental stress

Precipitating factors known to induce DKA are given in Box 1.

Present-day management has reduced the mortality of severe DKA and coma to 5%. Remarkably enough, there has been no further reduction in mortality. Further reduction is only possible if ketoacidosis is recognized early and treated promptly.

Pathophysiology[3]

Physiopathology of DKA is in essense a severe insulin deficiency combined with an excess of hormones that increase the blood glucose levels. Thus, insulin deficiency is associated with an increase in glucagon. This change in the insulin-glucagon ratio alters carbohydrate, fat and protein metabolism. In addition, due to the marked increase in glucagon levels, there is also a significant increase in the level of stress hormones including cortisol, growth hormones and catecholamines.

Insulin lack is furthermore associated with a varying degree of resistance to the action of insulin in DKA. The net result is an enhancement of the hyperglycemic state. Glucagon acts predominantly on the liver. It increases the activity of carnitine acyltransferase I, and enhances transport of long chain fatty acids into the mitochondria. Cortisol increases gluconeogenesis and promotes insulin resistance. Catecholamines enhance lipolysis and ketogenesis, and also accelerate gluconeogenesis. Growth hormone also increases lipolysis and contributes to insulin resistance.

Hyperglycemia

This as has already been explained is chiefly due to a marked increase in glucose production in the liver (gluconeogenesis). It is also in part due to poor utilization of glucose by the tissues. A factor that determines the degree of hyperglycemia in DKA is the extent of glucose loss through the kidneys. As long as the circulatory state is satisfactory and the kidneys remain well perfused, there is a ready leak of glucose from the blood and the extracellular space via the urine. This helps to limit hyperglycemia. Volume depletion could however lead to impaired renal perfusion, a lowered urine output and consequently a diminished leak of glucose in the urine. This could result in a sharp increase of glucose in the extracellular space, even though the hepatic glucose production remains unchanged.

Ketosis and Metabolic Acidosis

Ketosis is chiefly due to increased lipolysis in fat depots providing a source of free fatty acids as fuel. These free fatty acids are converted to ketones under the influence of glucagon. The predominant ketoacids are beta-hydroxybutyrate and acetoacetic acid, the ratio of these two ketoacids being 3:1.

Metabolic acidosis in uncontrolled diabetes is due to—

- *Uncontrolled ketosis with ketonemia* This results in an increase in the anion gap because of the buffering by bicarbonate of the hydrogen ion.
- *Hyperchloremic acidosis* Many patients have a reduction in bicarbonate which is in excess of the increase in the anion gap. This indicates the association of a non-anion gap hyperchloremic acidosis. The latter has been recognized for quite some time as a complication occurring in the later treatment stages of DKA. It may however also occur early, particularly in patients who are not so severely volume depleted. It is important to recognize hyperchloremic acidosis as it takes longer to resolve compared to acidosis due to increased ketones in the blood. This is because ketoacids are metabolized to generate equimolar quantities of bicarbonate, while hyperchloremic acidosis stands corrected only through increased generation of bicarbonate by the kidneys.
- *Lactic acid acidosis* Increased lactic acid production contributes to the metabolic acidosis of severe DKS, when tissue perfusion is impaired because of a poor circulatory state.

Fluid and Electrolyte Abnormalities

Fluid and electrolyte loss form an important feature of DKA. This loss is consequent to the osmotic diuresis produced by glycosuria that follows from severe hyperglycemia. Fluid loss may amount to 4–8 L in an average patient. There is also a marked depletion of sodium, potassium and chloride that may amount to 300–600 mEq or more. Phosphates and magnesium are also lost but in smaller quantities. The degree of electrolyte loss may not be manifested in the serum electrolyte levels, which may be only slightly reduced in concentration. Hyponatremia may, however, be observed. Hypernatremia pointing to excessive water loss, in comparison with sodium loss, is rare. This is because of the shift of water from the intracellular compartment to the hyperosmolar extracellular and vascular compartments. The hyperosmolarity of the extracellular space, which induces this shift, is due to hyperglycemia. Shift of water from the intracellular compartment is accompanied by a shift of potassium from the cells into the interstitial and vascular compartments. Metabolic acidosis accentuates the shift of potassium from the intracellular to the extracellular compartment. Serum potassium levels may thus be normal or high, in spite of a gross overall deficit of potassium in the body. Chloride loss in the urine is less than the sodium loss, because sodium is additionally lost as an accompanying cation when ketones

are excreted in the urine. Serum chloride concentration may thus not be significantly reduced.

Altered Mental State

This has not been well explained in patients with DKA. In all probability, altered mentation, obtundation, drowsiness and coma are at least partly related to serum osmolality. Patients with an altered mental state have an osmolality more than 350 mOsm/L. Ketonemia with metabolic acidosis also probably contributes to the altered mentation.

Clinical Features[3]

Nausea and vomiting are frequent presenting manifestations, and may precede drowsiness and coma by a few days. Abdominal pain may also occur and, in some patients, is severe enough to mimic an acute abdomen. Respiration is of Kussmaul's type, deep and labored, and there is a fruity smell of acetone in the breath. A history of polyuria, polydipsia, polyphagia and muscle cramps in the immediate past may be given by the patient or his relatives. The mental state is often confused and obtunded. Drowsiness progressing to coma can occur over a few hours to a few days.

Clinical examination reveals evidence of dehydration. The skin is dry, inelastic, and the tongue dry and furred. The eyeballs are soft; there is tachycardia, hypotension and oliguria. The untreated patient often progresses to drowsiness and coma from which he cannot be aroused by even the most painful stimuli. The corneal reflexes may then be lost, and the plantars become extensor. The blood pressure continues to drop, so that terminally it is unrecordable. Death results from peripheral circulatory failure or cardiac arrest.

Severe DKA is often triggered by precipitating factors, the main ones being acute infection, omission of insulin due to vomiting or diarrhea, or to poor food intake, and poor compliance. Important precipitating factors have already been listed in Box 1.

Laboratory Investigations

The urine shows glycosuria and ketonuria. The blood shows hyperglycemia, the blood sugar usually being more than 450 mg/dL. It is, however, important to stress that severe hyperglycemia is not always present. In the presence of acidosis, the diagnosis should be suspected even if the blood sugar levels are not very high. This is particularly observed in patients who eat poorly and imbibe a large quantity of alcohol, and in pregnant females. In the latter, blood sugar levels may occasionally be modestly elevated even in the presence of severe ketoacidosis.

Ketonemia is present, and the presence of metabolic acidosis is mirrored by a sharp fall in arterial pH (to below 7.3 and, at times, <7.0), a fall in the bicarbonate content (often <10 mEq/L), an increase in the anion gap, and by a marked increase in the base deficit as computed by the Astrup technique. There is compensatory hypocapnia.

There are some points to be noted in relation to acidemia and ketonemia in DKA—

- A deceptively mild acidemia may be observed in DKA if there has been sufficiently severe vomiting to produce a metabolic alkalosis. The latter neutralizes the effect of metabolic acidosis. Mixed acid-base disturbances should, therefore, be correctly interpreted with reference to the clinical findings.
- Absence of ketones in a patient with acidosis, hyperglycemia and volume depletion, should suggest predominance of beta-hydroxybutyric acid as the predominant ketone in the plasma. In the presence of lactic acid acidosis (due to hypoperfusion), the acetoacetate is largely converted to beta-hydroxybutyrate. The nitroprusside test (a semiquantitative test) only recognizes acetone and acetoacetate, so that ketonemia due to beta-hydroxybutyrate may go undetected. In these patients, treatment with insulin and fluid replacement reduces the ketonemia. Beta-hydroxybutyrate is first converted to acetoacetic acid before being metabolized. Paradoxically thus, though the patient is improving, the nitroprusside test will now show a stronger positivity to plasma ketones. A clinical assessment, and monitoring of the pH of arterial blood, gives the correct perspective in these patients.

The blood urea, creatinine and nonprotein nitrogen (NPN) are generally elevated; the azotemia is prerenal due to dehydration and also due to endogenous tissue breakdown. Serum sodium and chloride are generally modestly reduced. Hyponatremia is occasionally more marked, in which case the serum sodium is less than 125 mEq/L. Very rarely, one encounters hypernatremia when water loss significantly exceeds sodium deficit. The serum potassium in majority of untreated cases is normal or slightly elevated, even though there is an overall deficit in body potassium. Some patients may, however, present with hypokalemia right from the start. Hypokalemia is often present during treatment with insulin. Less than 10% of patients have hypophosphatemia to start with; 10% of patients may also present with hypomagnesemia. Hypocalcemia is frequent and the serum invariably shows hyperosmolality.

Well-marked leukocytosis is often present (15,000–30,000/mm^3) even in the absence of infection (Box 2).

Diagnosis[3]

The most important clinical differential diagnosis is a hypoglycemic coma due to insulin reaction or an overdosage with oral antidiabetic drugs. Severe sweating is the hallmark of hypoglycemic coma. Twitchings, seizures, the presence of a decerebrate state and even neurological focal signs are observed with hypoglycemic coma, but not in diabetic coma. Deep-labored breathing with a fruity odor of ketones in the breath should further help distinguish DKA from hypoglycemic coma. When doubt exists, blood should first be withdrawn for estimating the blood glucose level, and 50 mL of 50% dextrose is then injected intravenously. The patient

Box 2: Laboratory and other tests

- Laboratory tests—
  - CBC, ESR
  - Urine (sugar, ketones, pus cells, RBCs and casts)
  - Blood sugar (hyperglycemia)
  - Serum electrolytes (usually hyponatremia, serum K^+ normal or high to start with or low during treatment)
  - Blood urea, creatinine, NPN (usually raised)
  - Arterial pH, blood gases (pH <7.3, increased anion gap, bicarbonate <15 mEq, increased base deficit, ketonemia)
  - Serum Mg, Ca and phosphate (variable, may be low)
- Test for hyperosmolality
- Test for any precipitating factors
- ECG
- X-ray chest
- USG abdomen and pelvis

Abbreviations: CBC, complete blood count; ESR, erythrocyte sedimentation rate; RBC, red blood cell; NPN, nonprotein nitrogen; Mg, magnesium; USG, ultrasonography.

becomes alert quickly in hypoglycemic coma, but remains unchanged in diabetic coma.

Ketonuria and ketonemia can also occur in starvation and following alcohol ingestion.[4] There is no glycosuria in starvation ketosis, the blood sugar is normal or low, and the ketonemia is very mild.

Alcoholic ketoacidosis may occasionally bear a strong resemblance to DKA. There is well-marked ketonemia and ketonuria, but blood sugar levels are normal or low. Severe diabetics, who eat poorly and continue to ingest alcohol, may have severe DKA with only modest elevations in blood sugar levels.

Coma due to metabolic acidosis with a large anion gap may also occur in uremia and in some poisonings (notably methyl salicylate poisoning). The absence of ketonemia and ketonuria in these conditions, and a careful clinical and laboratory assessment, clarify the diagnosis.

A diabetic patient may become comatose following a head injury or a cerebrovascular accident. A subarachnoid hemorrhage in a diabetic is often missed, and the patient is treated for diabetic coma. This is because of the increase in hyperglycemia triggered by the bleed. Neck stiffness, a positive Kernig's sign, and continuing drowsiness after correction of metabolic abnormalities, point to the correct clinical diagnosis. Imaging of the head further clarifies the diagnosis.

Finally, ketoacidosis with coma in a diabetic should be distinguished from the rare hyperglycemic hyperosmolar nonketotic coma.

Principles of Management

The principles of management are as follows—

- *To administer sufficient insulin intravenously,* so that acidosis is corrected and the blood sugar is brought down to near normal levels. Insulin corrects hyperglycemia and ketosis by correcting the basic abnormalities in metabolism—it stops ketogenesis and lipolysis, reduces neoglucogenesis, and increases the peripheral utilization of glucose.
- *To replace the loss of water and electrolytes* which characterize the severe diabetic state. Dehydration is corrected by rapid intravenous infusions of normal saline (N-saline), and hypokalemia, which is often encountered during recovery from diabetic coma, by a monitored infusion of potassium chloride.
- *To correct severe metabolic acidosis* Insulin is mandatory for this purpose; the use of IV sodium bicarbonate is avoided as far as possible, as it probably does more harm than good. It may be used only as an emergency measure in patients who are deeply unconscious and severely acidotic.
- *To correct shock, if present, by the emergency infusion of plasma or colloids* The circulatory hemodynamics will ultimately stand corrected only if adequate replacement of fluid and electrolytes is quickly achieved.
- *To determine the precipitating factor causing severe DKA* with coma, and to treat this factor. It is extremely important to search for infection, a common and important precipitating factor.
- *To monitor patients carefully* and meticulously through all phases of management.

Details of Management[3,5]

There is one important feature that needs to be emphasized in the management of diabetic ketosis and coma. This dangerous metabolic abnormality had a high mortality almost up to the end of the 20th century. This was felt to be due to three factors—

1. Overenthusiastic and very rapid replacement of IV fluids in an attempt to quickly correct volume depletion.
2. Frequent use of IV bicarbonate to help correct acidosis
3. Overenergetic use of IV insulin so that the blood sugar was brought down too rapidly.

It is believed that all these factors predispose to the development of cerebral edema, which is the main cause of death in DKA and coma.

An awareness of these factors in management has reduced the present-day mortality to less than 5%.

Monitoring the Patient

Close monitoring is important for easy and successful management. Once the diagnosis of diabetic coma is established, blood is withdrawn form a peripheral vein through a large needle, and sent for estimation of glucose, ketones, electrolytes, urea, creatinine, blood counts and other relevant biochemical tests. Twenty-five units of actrapid insulin are injected through the same needle; this is followed by the starting of an IV infusion of N-saline. Arterial blood is also promptly collected and sent for measurement of arterial pH, blood gases and bicarbonate content. It is important to

secure a good peripheral vein immediately after admission. In addition, a central venous line is secured with the venous catheter in the superior vena cava. This allows infusion of fluids, as well as measurement of the central venous pressure. In patients who are markedly hypotensive from fluid and electrolyte loss, it is best to secure one more peripheral vein to aid in the rapid replacement of fluids.

A nasogastric tube is passed into the stomach, which is washed out by sodium bicarbonate. A Foley's catheter in the bladder allows the maintenance of an hourly urine output chart, as also examination of the urine for sugar and ketones.

Comatose patients have no control over their airways and often aspirate. They should be intubated and, if need be, given ventilator support.

The patient should be monitored as for any critical illness with special emphasis on intake-output charts, vital signs, evidence of pulmonary congestion, serum electrolytes, renal function, and above all, blood glucose and plasma ketones.

Blood glucose should be monitored hourly at the bedside, and 2–3 hourly in the laboratory. This initially provides information as to whether the insulin administered is adequate to cause a fall in the high blood glucose levels at the rate of 75–100 mg/dL per hour. Later, estimating the blood glucose enables the physician to adjust insulin administration so that blood glucose levels are maintained between 150 mg/dL and 250 mg/dL, and both hypoglycemia and a return to hyperglycemia, are avoided. Arterial pH, blood gases and serum electrolytes are monitored as often as necessary. The latter should preferably be monitored every 4–6 hours till the patient is well on the way to recovery. All data should be charted on a flow sheet for easy evaluation.

Insulin therapy and volume replacement to correct dehydration should be carried out simultaneously.

Insulin Therapy

Intravenous infusion of insulin is promptly started, so as to allow a careful and not too rapid rate of fall in blood glucose. An IV bolus of 20–25 units of insulin is given, followed by an IV infusion of insulin in N-saline titrated so as to administer 6–8 units (0.1–0.15 units/kg) of actrapid or huminsulin S insulin per hour. This can be achieved by adding 50 units of soluble insulin (actrapid or huminsulin S) to 50 mL of N-saline (i.e. 1 U/mL) and delivering this intravenously through a syringe pump either through a separate vein or "piggy-backed" into an IV fluid line. As mentioned above, initially 6 units/hour or 6 mL/hour is given and once the blood sugar starts to fall, the rate of infusion is titrated so that the blood glucose falls at the rate of 3–4 mmoL/hour. A trend of the rate at which blood glucose falls is evident in 3–4 hours. A faster rate of fall is unnecessary and perhaps may even be harmful, as it can cause hypoglycemia or even contribute to or precipitate cerebral edema.

A sliding scale (based on an hourly measurement of blood glucose) of insulin requirement that generally works is as follows—

- If blood glucose is less than 5 mmoL/L (90 mg/dL) give 0.6 units/hour.
- If blood glucose is less than 10 mmoL/L (180 mg/dL) give 2 units/hour.
- If blood glucose is more than 10 mmoL/L, give 4 units/hour.

An alternative method of delivering insulin (other than through a syringe pump) is to dilute 50 units of soluble insulin in 500 mL of N-saline and regulate delivery at the desired rate—of say 4–6 or more units per hour.

It is important to note that blood glucose and ketones will rise sharply if insulin delivery is intermittent. Close hourly monitoring of blood sugar is mandatory to start with. If the blood glucose fails to fall, it means that the infusion pump is not working or is turned off or the infusion cannula is blocked. Very occasionally the insulin requirement may be higher (8–12 units/hour to start with).

When the blood sugar levels are between 180 mg/dL and 200 mg/dL, a 5% dextrose saline infusion is started, but the insulin infusion is continued till ketosis clears. This is important as decreasing the insulin infusion at this juncture may result in a persistence of ketosis for a much longer period of time. A situation may well arise during the treatment of DKA, when the blood glucose level is normal or less than normal, and yet ketonemia and ketonuria are very evident. This is countered by an IV infusion of 5% or even 10% dextrose, and simultaneous continuation of the insulin infusion. It should never be forgotten that the main battle is to be waged against ketosis and resulting acidosis, which strongly disturb the homeostasis of the milieu interieur. Hyperglycemia is generally controlled within 12 hours; ketosis may take longer to be controlled (18–24 hours, or even more).

It is often difficult to determine when ketosis is controlled. Serum ketone measurements are useful, but positive tests for plasma ketones may persist well after acidosis is resolved. Perhaps this is because acetone is cleared more slowly than acetoacetic acid and beta-hydroxybutyric acid. The sodium nitroprusside test is a measure of the acetone in the plasma, and can give persistently positive readings for ketones, even though acetone does not alter acid-base balance. Therefore, to determine whether the ketosis has cleared, it is important to monitor the anion gap, and the arterial pH. An abolition of the anion gap and a normal arterial pH signifies the clearance or control of ketosis.

Once the patient is conscious, alert and able to eat or drink, IV fluids and IV insulin can be stopped and the patient is started on subcutaneous insulin. It is important to continue IV insulin infusion till the first subcutaneous injection of insulin has started to take effect (1 hour after actrapid insulin and 3–4 hours after a long acting insulin), else there may well be a sudden rebound increase in the blood sugar and ketones.

Fluid and Electrolyte Replacement

Severe DKA is always associated with fluid losses that may be as high as 4–8 L. However, slower fluid replenishment is now recommended compared to what was advised in earlier years.

It is vital to start fluid therapy immediately with N-saline. About 1–2 liters are given over 2 hours in patients who are not in shock. This is followed by another 1 liter over the next 4 hours. Further infusions of 4 liters may be necessary over the next 24 hours. To this is added fluid losses in urine and in vomit as observed over 24 hours.

Patients in shock as also oliguric patients may require further fluid replacement, with the use of plasma expanders to start with. On the other hand, in patients with heart failure, in those with fluid overload, or in patients suspected to have cerebral edema, fluid replacement should be slower.

Volume replacement needs to be individually assessed and often modified or adjusted in each patient on clinical grounds, and on central venous pressure readings. One has to be extra careful in older patients or in those with cardiac dysfunction for fear of inducing acute pulmonary edema.

Though N-saline is used initially for fluid replacement, 0.45% saline has been suggested to replace 1–2 liters of isotonic saline if there is marked hyperosmolality of the plasma (>350 mOsm/Ka) or in rare instances where there is marked hypernatremia (>150 mEq/L). This suggestion is debatable as the use of hypotonic saline may increase the intracellular movement of water which could well contribute to or precipitate cerebral edema.

Five percent dextrose solution should be substituted for N-saline when plasma glucose falls to 10–14 mmoL/L (180–250 mg/dL) to prevent hypoglycemia. IV insulin needs to be continued to counter ketosis and promote utilization of glucose in tissues.

Potassium replacement In the early stages of untreated diabetic coma, the serum potassium may be high in spite of a total body deficit of potassium. Once the DKA comes under control, hypokalemia often develops. This is due to the passage of glucose (and with it of potassium) from plasma to cells during conversion of glucose to glycogen under the influence of insulin, and also to a loss of potassium in urine following an improvement in urine output. Hypokalemia during recovery from DKA and coma should be corrected by a slow IV infusion of potassium chloride in dextrose. Generally, not more than 40–60 mEq of potassium are needed over 24 hours. Potassium administration must be monitored by electrocardiography and by checking the serum potassium levels periodically.

Phosphate administration Though phosphate levels in serum are known to fall during treatment of DKA, in our experience, replacement of phosphates is rarely necessary. There is, however, one group of patients in whom phosphate replacement is considered to be essential. This is a small group of probably less than 5–10%, who has hypophosphatemia (<1.5 mg/dL) at the time of admission. A further fall during treatment with insulin could lead to manifestations of hypophosphatemia. These include muscle weakness, respiratory failure due to respiratory muscle weakness, decreased myocardial contractility, hemolysis and rhabdomyolysis. Phosphate replacement during therapy is achieved by adding 5–10 mL of potassium phosphate solution (3 mmoL/mL) to the replacement fluids used for replenishing the hypovolemic state. About 1–4 mL of potassium phosphate are added to 1 liter of N-saline. Phosphate administration may occasionally produce a fall in serum calcium with resulting tetany. Serum calcium levels are monitored, and a drop in the serum calcium is treated by IV administration of 10–20 mL of 10% calcium gluconate.

Use of Sodium Bicarbonate

Metabolic acidosis is invariably corrected with insulin therapy. Sodium bicarbonate should, therefore, not be used to combat acidosis. In fact, bicarbonate therapy often can do more harm than good. The complication of cerebral edema is more likely in diabetic ketoacidotic children treated with IV sodium bicarbonate. IV bicarbonate contrary to popular belief may not improve intracellular acidosis as cell membranes are impermeable to HCO_3 ions. In fact, CO_2 can enter into cells and combine with H_2O to form H_2CO_3, which may dissociate to H^+ and HCO_3, thereby aggravating the acidosis. Bicarbonate therapy can also result in sodium overload, hypocalcemic tetany, a fall in pH in the cerebrospinal fluid and a rebound metabolic acidosis.

The only indication for IV bicarbonate is a pH less than 7.1, as this poses an immediate threat to life. A pH less than 7.1 can cause myocardial dysfunction, cerebral depression, intractable hypotension, resistance to insulin and tissue cell injury. About 100 mmoL of sodium bicarbonate in 400 mL distilled water is given at the rate of 200 mL/hour to counter a pH less than 7.1. The routine use of bicarbonate in DKA is unnecessary and perhaps harmful.

Treatment of Circulatory Collapse

In addition to the rapid infusion of N-saline, it may be necessary to use colloids—albumin and other plasma expanders—to counteract severe shock and urgently increase the volume within the vascular compartment. Vasopressors should be avoided as far as possible, as increasing the degree of peripheral vasoconstriction worsens tissue hypoxia; also catecholamines like nor-epinephrine make glucose control even more difficult as they act counter to insulin.

Detection and Treatment of the Precipitating Factor

It is important to determine the precipitating factor causing DKA and coma. An acute infection, like pneumonia, a lung abscess, a carbuncle or acute dysentery, should be recognized and treated. It is to be noted that though well marked DKA can by itself cause a significant leucocytosis (up to 20,000/mm^3), fever does not occur in these patients in the absence of infection. The presence of fever is an indication for the use of empiric antibiotic therapy if the source of infection is unidentified.

Meticulous Nursing and Critical Care

This is vital for survival. Frequent changes in posture are imperative, and a clear airway should be maintained at all

Box 3: Important complications of diabetic ketoacidosis and coma

- Hypoglycemic coma (overuse of insulin)
- Irreversible shock and circulatory failure
- Sudden death due to cardiac arrest or ventricular fibrillation, generally due to hypokalemia
- Acute myocardial infarction, or cerebrovascular accident
- Cerebral edema
- Acute lung injury and acute respiratory distress syndrome
- Acute vascular insufficiency in one or both lower limbs, particularly in older patients with atherosclerotic disease
- Acute renal shutdown
- Aspiration pneumonia
- Thromboembolism, particularly in older patients
- Infections

costs, as hypoxia due to ventilation-perfusion mismatch worsens the prognosis.

Complications during Treatment of Diabetic Ketoacidosis and Coma

Important complications of DKA and coma are described below (refer Box 3)—

- An overdose of insulin can result in hypoglycemic coma. A frequent periodic check of blood glucose should prevent this problem. Severe sweating in a patient being treated with insulin for DKA should always suggest the possibility of insulin-induced hypoglycemia. The use of 5% dextrose solution covered by insulin when blood glucose levels have fallen substantially has already been mentioned.
- Irreversible shock and circulatory failure may complicate the course of diabetic coma. This is observed when patients are brought in very late, and when severe tissue hypoxia has been present for a prolonged period.
- Sudden death due to cardiac arrest or ventricular fibrillation during recovery from diabetic coma is generally due to hypokalemia. Frequent ventricular ectopics during recovery should suggest hypokalemia. Severe hypophosphatemia may potentiate the effects of hypokalemia.
- Acute myocardial infarction or a cerebrovascular accident may occasionally complicate the course of diabetic coma. Failure to recover consciousness after ketosis has been controlled should suggest the possibility of a stroke. The persistence of shock after rapid correction of fluid, electrolyte and metabolic abnormalities should make one suspect a myocardial infarction or pulmonary embolism.
- Cerebral edema[6] is a dreaded complication. It is manifested by a deteriorating level of consciousness when the metabolic complications (including ketosis) show clear evidence of improvement. It accounts for 50% of fatalities, especially in children. It is thought to result from shifts of water and ions into the brain, particularly of water into dehydrated hypertonic brain cells when relatively hypotonic fluid reaches the extracellular compartment. Administration of hypotonic saline intravenously may perhaps aggravate this condition.

  Risk factors for cerebral edema include: (1) excess fluid replacement and fluid replacement given far too rapidly; (2) over-rapid fall in blood glucose—hence, the wisdom of using a 5% of dextrose solution together with insulin when the blood sugar approaches 200 mg/dL; (3) high doses of insulin (than those recommended) to reduce blood sugar. Why and how the last factor operates is unknown; perhaps insulin can affect various ion transport mechanisms in the brain.

  Increasing cerebral edema besides causing increasing decline in the conscious state (even after metabolic abnormalities are corrected) ultimately leads to coning and cardiovascular arrest.

  Well-marked cerebral edema is generally fatal, with a mortality as high as 90%. IV mannitol (0.2 g/kg over 3 hours) is recommended; this is repeated if there is no improvement. Dexamethasone may be used but is not thought to be of any benefit.
- A rare complication of ketoacidosis is acute respiratory distress syndrome (ARDS).[7] This is generally observed in older patients and is invariably triggered by excessive volume replacement. Other unknown factors are also probably responsible for contributing to increased pulmonary capillary permeability. Acute lung injury manifests with noncardiogenic pulmonary edema and refractory hypoxia that needs ventilatory support as outlined in the ARDS network trial. Under the above circumstances, it has a forbidding mortality.
- Recovery from coma can be complicated by acute vascular insufficiency in one or both lower limbs. This is particularly likely to occur in old patients with atherosclerotic disease, following prolonged hypotension.
- Acute renal shutdown may complicate recovery from DKA and coma.
- Aspiration pneumonia, particularly in obtunded and comatose patients, is a common complication of DKA.
- Thromboembolism may be a complication, particularly in older patients. Arterial thrombosis, if it occurs, chiefly involves the lower limb vessels. Femoral vein thrombosis is an important cause of sudden death from massive pulmonary embolism.
- *Infections* Diabetic patients are prone to infection. Urinary tract infections and respiratory tract infections are common. Nosocomial sepsis with positive blood culture is occasionally encountered. A rare but frequently fatal infection in severe diabetes and DKA is mucormycosis, caused by the fungus *Rhizopus*. The presence of a black necrotic area around the eye, nasal cavity, nose, or the presence of conjunctival injection with circumocular edema and sinusitis are strongly suggestive of mucormycosis. Proptoses of the eyes with restricted ocular movements are late features. This fungus has a tendency to invade vessels causing thrombosis and infarction. Unless recognized very early and promptly treated, death generally ensues.

Table 1: Differences in laboratory features between diabetic ketoacidosis and hyperglycemic nonketotic hyperosmolar diabetic syndrome

	HNHS	*DKA*
Blood glucose level	Very high; often >700 mg/dL	Generally not so high; 350–450 mg/dL
Serum Na	Hypernatremia ; Often >150 mEq/L	Hyponatremia often present; Hypernatremia rare
Osmolality	Marked >350 mOsm/kg	Less marked; generally <350 mOsm/kg
Ketonuria	Absent	Present
Ketonemia	Absent	Present
Anion gap	Normal	Marked
Renal dysfunction	Generally present—well marked	May be present

Abbreviations: HNHS, hyperglycemic nonketotic hyperosmolar diabetic syndrome; DK, diabetic ketoacidosis.

Hyperglycemic Nonketotic Hyperosmolar Diabetic Syndrome[3,8]

This is a rare cause of coma in diabetes. In its typical form, it is characterized by marked hyperglycemia (often >700 mg/dL), with little or no reduction in the plasma bicarbonate. There is also marked hypernatremia with serum sodium levels over 150–155 mEq/L. The plasma shows no ketonemia and ketone bodies in urine are absent. In the typical case, ketosis does not develop because insulin levels in blood are sufficient to suppress lipolysis and ketogenesis. These patients generally are elderly with type II diabetes.

A large overlap, however, exists in the clinical presentation of DKA and hyperosmolar nonketotic diabetic coma. Thus, there are patients with hyperosmolar coma who have a fair degree of ketoacidosis, just as there are patients with typical ketoacidosis with significant hypernatremia and hyperosmolarity.

Hyperglycemic nonketotic hyperosmolar diabetic syndrome is much less common than DKA and has a higher mortality, perhaps due to associated comorbidity in elderly patients, late diagnosis and improper treatment.

Precipitating factors include stroke, myocardial infarction, infection, renal dysfunction, use of glucocorticoids and use of thiazide diuretics. Mental obtundation, dementia, physical disability and any cause that reduces access to the drinking of water are often present in these elderly patients. The differences in laboratory features between DKA and HNHS are tabled in Table 1.

Presentation

- Symptoms caused by hyperglycemia include thirst, polyuria, weight loss but without features of ketoacidosis.
- Dehydration with hypotension; tachycardia may not be evident in elderly patients.
- Oliguria with raised creatinine, urea, NPN levels in blood.
- Confusion, drowsiness, disorientation and even coma.
- Complications of HNHS may be the presenting feature—these include thrombotic events, chiefly stroke manifesting with hemiparesis. Seizures may complicate the syndrome or be a presenting feature. Other thrombotic events include peripheral arterial occlusion, venous thrombosis, pulmonary embolism. These thrombotic events are due to dehydration plus increased blood viscosity.

Management[3]

Management is similar to that of DKA—

- *Insulin* Insulin is given exactly in the manner outlined for DKA. Hyperglycemia is generally easily controlled.
- *Correction of dehydration* Fluid replacement should start with N-saline or ringer lactate solution. This is followed by a replacement of the water deficit by half-strength saline or dextrose solution covered adequately with insulin, in the presence of a marked increase in plasma osmolality (>350 mOsm/kg) or marked hypernatremia. Saline replacement should be cautious and carefully monitored in elderly patients with cardiac disease.
- *Potassium replacement* Many patients have a potassium deficit. Potassium replacement, if necessary, should be given with careful monitoring of serum potassium at frequent intervals.
- *Low molecular weight heparin* Enoxaparin 0.4 mg subcutaneously once a day prophylactically is often advised. Full anticoagulation should only be given in the presence of thromboembolic complications. The risk of bleeding in these patients is high.
- *Intercurrent infections and other precipitating factors should be identified and treated.*

Most patients after recovery can be weaned off insulin and given oral antidiabetic medications.

Neurological Complications of Hyperglycemic Syndromes

Neurological complications with varying frequency can occur in both DKA and HNHS. It is important to be aware of these complications, as they may occur during the phase of metabolic derangement and, in some instances, after correction of the metabolic state. Though touched upon briefly (cerebral edema has already been discussed at length) in the descriptions of DKA and HNHS, these complications are discussed in a little more detail in this section.

Altered Mentation

This has been briefly mentioned in the pathophysiology of DKA. It is also frequently observed in the HNHS.

Drowsiness, progressive obtundation progressing to unconsciousness and coma are the usual abnormalities in DKA. Coma may be so deep that the patient is totally

unresponsive to painful stimuli. Reflexes are generally lost, plantars may be extensor. The corneal and papillary reflexes are generally present and are lost terminally.

Generally, there are no lateralizing signs. If present, a CT of the brain is mandatory. An unconscious state persisting after correction of metabolic abnormalities necessitates both a CT of the head and a toxicology screen.

It is to be noted that there is no good correlation between the degree of hyperglycemia, the degree of metabolic acidosis, the osmolality and the mental state.

Less commonly, the mental state is that of excitability, delirium accompanied by delusions and hallucinations, particularly if drug intoxication or alcohol has precipitated the metabolic abnormality. These patients may be very difficult to manage and require to be sedated with tranquilizers so as to allow treatment of the metabolic abnormalities.

Cerebral Edema

This has been discussed at length in DKA. It can also occur in patients with HNHS. Cerebral edema in children with DKA is associated with a marked increase in mortality.

Focal Neurological Deficits

Strokes due to thrombotic episodes and intracerebral hemorrhage are important complications and, at times, presenting features of HNHS. Intracerebral venous thrombosis has been reported[9] and has a poor prognosis.

Many focal neurological signs particularly in HNHS disappear after recovery from the syndrome. It is possible that they represent focal areas of poor cerebral perfusion unmasked by dehydration and increased viscosity.

Correction of fluid and electrolyte abnormalities during treatment may rarely cause pontine and extrapontine myelinolysis.[10] This can be a cause of prolonged unconsciousness after metabolic recovery and may only be picked up by a good magnetic resonance imaging (MRI) of the head.

Seizures

Generalized or focal seizures are common in the HNHS and may be resistant to the usual anticonvulsants.[11] Epilepsia partialis continua is a rare seizure disorder observed in both DKA and HNHS.[12]

Cognitive Impairment

Cognitive impairment is more common in elderly patients and may occur even after recovery from either DKA or HNHS. It may be related to a neurological deficit or it may occur without any evidence of a neurological deficit. If not caused by structural damage, it invariably improves with time.

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CHAPTER 61

Neurological Problems

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A. RAISED INTRACRANIAL PRESSURE

Jimmy Lalkaka, BS Singhal

INTRODUCTION

Many neurological diseases cause an elevated intracranial pressure (ICP). Left untreated, it leads to cerebral ischemia, brain herniation and death. Therefore, early recognition and appropriate management of raised ICP remains the cornerstone of Critical Care Neurology. An ICP of more than 20 mm Hg for more than 10 minutes indicates an elevated ICP.[1] The time period mentioned above is to exclude transient elevations of ICP which occur during suctioning, straining and positioning of the patient. A sustained ICP greater than 40 mm Hg is a life-threatening emergency.[2]

PATHOPHYSIOLOGY

In simple terms, ICP is defined as the pressure that exists within the skull vault in relation to the atmospheric pressure. Normal ICP is 5–15 mm Hg in adults and older children in supine position. The Monro-Kellie doctrine helps us to understand the concept and dynamics of ICP. According to this doctrine, the skull is a rigid closed box, containing three noncompressible elements—brain tissue (80%), cerebrospinal fluid [CSF (10%)] and blood (10%). These three components are in a state of dynamic equilibrium with each other, so that the overall volume remains constant. Any increase in volume of one element is compensated for by a decrease in the volume of the other two. This compensatory measure is called intracranial compliance. It effectively maintains ICP at normal levels during the early stage of intracranial pathology. For instance, an initial mild increase in the size of a mass lesion will not produce much change in ICP because CSF and blood are displaced with a decrease in the volume of these elements. Measures like CSF drainage and hyperventilation reduce elevated ICP by reducing intracranial volume of CSF and blood respectively. However, with further increase in size of the lesion, intracranial compliance and compensatory mechanisms begin to fail, so that even a small increase in volume causes a dramatic elevation of ICP (Fig. 1). The extent of rise in ICP also depends on the rate at which the intracranial volume increases. A sudden rise in intracranial volume raises ICP to a greater level than a gradual increase in volume. This explains why an acute hematoma raises ICP more significantly than a slowly growing brain tumor. The type of added volume also has a differing influence on the ICP. Addition of equal volume of CSF and tumor mass does not raise ICP equally. CSF may be quickly moved down the spinal theca or absorbed into the blood, whereas a tumor is not so easily displaced and may obstruct CSF pathways, further raising the ICP.

A normal ICP is required to ensure adequate blood flow to the brain with optimum supply of oxygen and glucose to brain tissue. The cerebral blood flow (CBF) in turn depends on the driving pressure called cerebral perfusion pressure (CPP) which maintains normal circulation across the capillary beds of the brain. Conventionally, CPP is defined as the difference between mean arterial pressure (MAP) and mean ICP.

CPP = MAP – ICP (MAP = 1/3 systolic BP + 2/3 diastolic BP)

Cerebral autoregulation maintains CPP at a constant level over a wide range of MAP of 50–150 mm Hg, presuming that the ICP remains within normal limits. This is achieved by

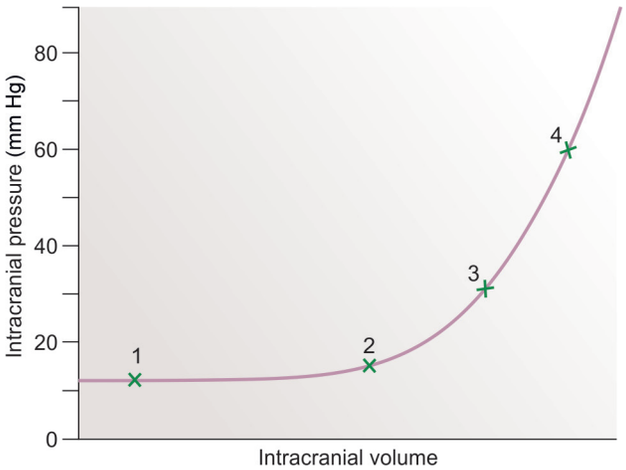

Fig. 1: Illustration of the relationship between intracranial volume and intracranial pressure. Note that beyond point 3, even a small increase in the intracranial volume produces a marked elevation of intracranial pressure

adjustments in cerebral vascular resistance. A fall in MAP causes vasodilatation of arterioles in the brain to increase CBF, while a rise in MAP produces arteriolar vasoconstriction to prevent hyperperfusion. Below a MAP of 50 mm Hg, autoregulation fails, CPP falls with reduced CBF and resultant ischemia. When ICP is increased, the CPP is reduced. However, cerebral autoregulation helps to maintain constant CBF despite reduction in CPP. However, when CPP falls below 50 mm Hg, the cerebral autoregulatory mechanism becomes exhausted and CBF falls. Cerebral tissue oxygenation suffers and neuronal ischemia results.

ETIOLOGY

Lesions with Focal Mass Effect

They include brain tumors, large cerebral infarcts, intracranial hemorrhage and cerebral abscess. The ICP in these conditions is maximum locally, due to dural partitions which cause compartmentalization of the mass and resultant tissue shifts.

Generalized Brain Edema

They include hypoxic-ischemic encephalopathy, head injury (diffuse axonal injury), acute subarachnoid hemorrhage, meningitis and encephalitis, prolonged status epilepticus, hypertensive encephalopathy and metabolic derangements (hyponatremia, hepatic and renal encephalopathy). Here the increased ICP is evenly distributed throughout the brain and tissue shifts are minimal.

Obstruction of CSF Pathways

Hydrocephalus results from obstruction of CSF pathways within the ventricles or in the subarachnoid spaces at the base of the brain. Common causes of hydrocephalus include meningitis (especially tuberculous and fungal), subarachnoid hemorrhage, cerebellar, thalamic or intraventricular hemorrhage, posterior fossa tumors and normal pressure hydrocephalus.

Increase in Cerebral Venous Pressure

It is caused by cerebral venous sinus thrombosis or jugular vein thrombosis.

CLINICAL FEATURES

Raised ICP causes brain disturbance in the following ways—

- Global hypoxic-ischemic damage caused by reduced CPP and CBF.
- Mechanical compression, shift and herniation of brain tissue due to ICP gradients across the brain compartments.

The clinical features of raised ICP vary depending on whether the underlying pathological process is focal, causing a localized mass effect, or generalized, with a diffuse rise in ICP.

Generalized Brain Edema

The elevated ICP is distributed evenly throughout the brain. Early symptoms of raised ICP are headache and vomiting. The headaches may be worse in the supine position and aggravated by coughing and valsalva maneuver. Vomiting can be projectile. Altered sensorium may follow, ranging from mild confusion and increased irritability to drowsiness and stupor. It is caused by global cerebral ischemia, once the ICP rises high enough. Diplopia due to unilateral or bilateral sixth cranial nerve palsy may also occur. The presence of papilledema signifies raised ICP of some duration. The Cushing's reflex (hypertension, bradycardia and irregular breathing) indicates severe intracranial hypertension.

Focal Mass Effect

Mass lesions initially present with focal sensorimotor deficits depending on the location of the lesion. Clinical features of raised ICP follow and are similar to those with generalized brain edema. In addition, these mass lesions can cause fatal brain herniation. A major pressure gradient between the different brain compartments causes displacement of brain structures from one compartment to another. This causes mechanical damage to the compressed surrounding brain tissue and also results in cerebral infarction due to compression of the anterior or posterior cerebral arteries against the edge of the falx or tentorium cerebelli. These devastating effects may not be accompanied by a significant elevation in global ICP, as the lesions initially remain confined to a localized compartment.

An ipsilateral dilated, nonreacting pupil is seen in uncal herniation, in which laterally placed mass lesions cause the uncus of the medial temporal lobe to herniate through the tentorium. This pupillary dilatation is followed by a decline in consciousness with accompanying hemiparesis and decerebrate posturing. Central herniation due to diencephalic lesions causes a downward displacement of the diencephalon and midbrain. Depressed consciousness occurs early, followed

by bilateral, medium-sized nonreacting pupils, decorticate posturing and Cheyne-Stokes breathing. Diabetes insipidus may occur due to hypothalamic involvement. Transfalcine herniation occurs when frontal or parietal mass lesions push the cingulate gyrus under the falx, causing occlusion of the anterior cerebral artery with contralateral leg weakness and coma. Posterior fossa lesions cause cerebellar tonsillar herniation through the foramen magnum, compressing the medulla and upper cervical cord. Hypertension, bradycardia, coma and respiratory arrest quickly follow.

Hydrocephalus

Diffuse expansion of CSF spaces occurs in obstructive hydrocephalus, causing increased pressure on adjacent brain tissue. In addition to the features of raised ICP mentioned above, bilateral frontal lobe signs develop with gait apraxia, lack of initiative and sphincter incontinence. Pressure on the midbrain by the dilated third ventricle causes impaired up-gaze.

INTRACRANIAL PRESSURE MONITORING

Direct ICP monitoring is the most accurate method of detecting raised ICP. Clinical assessment can be unreliable in judging ICP. The absence of papilledema does not exclude raised ICP in patients with acute problems. Pupillary dilatation, bradycardia, altered sensorium and decerebrate posturing are unfortunately late signs of raised ICP, by which time permanent brain damage usually occurs. Besides, in stuporous and comatose patients, early signs of neurologic deterioration may be difficult to detect on clinical examination. The goal of ICP monitoring is early detection of abnormal physiologic events which allows clinicians to intervene before a significant loss of neurological function occurs. ICP measurement can also accurately monitor the efficacy of ICP lowering treatment.

Intracranial pressure monitoring is considered in patients with an acute neurological disorder associated with an increased risk of raised ICP and a worsening neurological examination. It is most commonly used in patients with severe traumatic brain injury (TBI). Criteria for ICP monitoring in severe TBI have been listed in the subchapter Traumatic Brain Injury of Chapter Neurological Problems. ICP monitoring is also considered in patients with large hemispheric infarcts, subarachnoid hemorrhage (Grade 3 or more) with radiological evidence of hydrocephalus, intraventricular hemorrhage and spontaneous intraparenchymal hemorrhage with Glasgow Coma Score (GCS) less than 9.

Types of ICP Monitors

The intraventricular catheter and the intraparenchymal device are the most commonly used ICP monitoring devices. ICP can also be monitored by transducers placed at subdural, subarachnoid and epidural sites. However, they are not very accurate and are rarely used.

The intraventricular catheter or external ventricular drain (EVD) remains the gold standard for ICP measurement.[3] The catheter is inserted into one of the lateral ventricles and connected to an external pressure transducer. It gives the most accurate measurement of ICP of all the devices and also enables CSF to be drained when ICP is raised. The EVD also offers a portal to introduce drugs directly into CSF. It however, carries a high risk of infection (ventriculitis), especially if it is kept for more than 5 days. Use of antibiotic-coated catheters has significantly reduced infection rates. There is also a small risk of parenchymal or intraventricular hemorrhage during catheter placement. EVDs may be difficult to place if there is associated ventricular compression with chinked ventricles in diffuse cerebral edema. Presence of a coagulopathy also rules out the use of this device.

The intraparenchymal device is also commonly used for ICP monitoring. The fiber-optic transducer is inserted into the brain parenchyma. It is easily placed and carries a very low infection rate of 1%. Parenchymal ICP monitoring is appropriate for patients with diffuse cerebral edema and small ventricles which make ventricular catheter insertion difficult. The ICP measurement with this device may be misleading if ICP is not uniform throughout the brain. So if there is increased local pressure in a brain compartment produced by a mass lesion, this device should be placed ipsilateral and close to the lesion.

Normal ICP Waveforms

They are modified arterial pressure waves timed to the cardiac cycle. They reflect a transient increase in cerebral blood volume (CBV) that occurs with each arterial pulse. Normally, three pulse waves are seen: (1) P_1—percussive wave, reflecting cardiac systole; (2) P_2—tidal wave, reflecting diastole and (3) P_3—dicrotic notch, reflecting emptying of cerebral vessels. Normally the P_2 wave is smaller than P_1, indicating good brain compliance. If the P_2 wave becomes larger than P_1, it signifies poor brain compliance and impending failure of compensating mechanisms, leading to raised ICP.

Pathological ICP Waveforms

Two types of pathologic ICP waves have been described—

1. *Lundberg A waves* They are arrhythmic plateau waves. They occur suddenly, reach levels of 40–80 mm of Hg and last 5–20 minutes. They are accompanied by concomitant reduction in CPP. They are always associated with raised ICP and may herald impending herniation.
2. *Lundberg B waves* They are rhythmic waves with an amplitude of 5–20 mm Hg, occurring every 30 seconds to 2 minutes and lasting 1–5 minutes. Although less dangerous than A waves, they indicate reduced intracranial compliance and may be harbingers of plateau waves.

MANAGEMENT OF RAISED INTRACRANIAL PRESSURE

The aim of lowering ICP is to ensure an adequate CPP to maintain normal CBF and to prevent secondary ischemic

injury. An ICP of 20 mm Hg and above requires treatment. The generally accepted goal in neurocritical care is to keep the ICP at less than 20 mm Hg and the CPP between 60 mm Hg and 90 mm Hg.[4] Measures for controlling ICP can be divided into those which rapidly reverse acute rise of ICP and those which maintain it within a reasonable range. The rapidly acting measures include hyperventilation, hyperosmolar therapy and CSF drainage. Maintenance therapy includes sedation, analgesia, control of BP and prevention of fever.

General Measures

The first step in management, after securing airway, breathing and circulation parameters, is to do a computed tomography (CT) scan of the brain. An intracranial mass like a subdural/extradural hematoma or a tumor may need to be surgically evacuated at the earliest. Patients with raised ICP must be managed in the ICU with qualified medical personnel and trained nursing staff. ICP monitoring should be instituted in the appropriate situation.

Blood sugar must be maintained in the normal range. Poor outcome has been reported with both hypoglycemia and hyperglycemia. Hyponatremia must be avoided as it increases cerebral edema. Fever increases metabolic rate by 5–7% per degree celsius rise in body temperature and worsens outcome in patients with raised ICP. The temperature must be reduced with judicious use of antipyretics, cooling blankets and antibiotics, if evidence of infection exists. Seizures also significantly worsen ICP and clinical outcome and must be treated promptly with intravenous lorazepam, followed by phenytoin/fosphenytoin or valproate.

An important step in choosing the appropriate treatment strategy is to identify the intracranial compartment that is responsible for the pressure elevation. For instance, if swelling of brain tissue is responsible, osmotherapy is preferred. If increased CSF volume (hydrocephalus) is present, then placement of an EVD to divert the CSF outflow is often the most effective treatment.

Specific Measures

Position of the Head

The patient must be nursed with the head elevated at about 30° to the horizontal. This ensures adequate cerebral venous outflow through the jugular veins. The head should not be turned to one side as it can cause kinking of the ipsilateral jugular vein. Tight constricting tapes or bands around the neck should also be avoided for the same reason.

Blood Pressure and Fluids

In patients with raised ICP, hypotension must be avoided as it reduces CPP and induces cerebral ischemia. Most cases of hypovolemic shock are due to blood loss or sepsis. The patient must be maintained in an euvolemic state with 0.9% normal saline or albumin. Central venous pressure (CVP) should be maintained around 10 mm Hg. Hypotonic fluids like 0.45% saline or 5% dextrose should be avoided as they increase cerebral edema. Blood loss should ideally be replaced by blood transfusions. If the patient remains hypotensive despite fluid correction, then vasopressor and inotropic agents like dopamine or noradrenaline are used. Noradrenaline is more predictable and efficient than dopamine, especially in septic shock.

Reactive hypertension commonly occurs with acute rise of ICP. It gradually reduces over the first few days and does not require aggressive therapy. A precipitous fall of BP must not be allowed to occur in the acute stage at any cost, as, in presence of raised ICP, this will further jeopardize CPP and result in cerebral ischemia. If hypertension persists for several days, it should be gradually reduced with appropriate antihypertensive drugs.

Mechanical Ventilation

Mechanical hyperventilation is a quick and effective, but short-lasting way of reducing ICP. It is best used as a temporary measure to reduce ICP prior to definitive treatment like surgery. The patient is intubated and put on a ventilator. Settings are adjusted to keep $PaCO_2$ levels at about 30–35 mm Hg. Reducing $PaCO_2$ causes cerebral vasoconstriction through serum and CSF alkalosis with reduction in CBV, CBF and decreased ICP. An initial reduction of $PaCO_2$ by 5–10 mm Hg produces a 25–30% reduction in ICP. Care should be taken not to reduce $PaCO_2$ levels below 25 mm Hg as that may induce cerebral hypoperfusion and ischemia. Ideally, simultaneous monitoring of CBF by measuring jugular venous oxygen saturation ($SjvO_2$) should be done during hyperventilation. An $SjvO_2$ less than 45% will indicate a critically reduced CBF and impending cerebral ischemia.

Ventilator settings should also be adjusted to prevent hypercarbia ($PaCO_2$ >45 mm Hg) which cause vasodilatation and trigger sudden ICP elevation. Patients in ventilatory failure require positive end-expiratory pressure (PEEP). However, PEEP tends to increase ICP as PEEP-induced expansion of intrathoracic volume limits the venous return. It is advisable to maintain PEEP at 5–10 mm Hg. Hyperventilation becomes ineffective after more than 6 hours due to the compensatory mechanisms for CSF alkalosis, so long-term hyperventilation is not beneficial.

Hyperosmolar Therapy

Hyperosmolar therapy with mannitol or hypertonic saline (HTS) causesa rapid reduction of ICP in the short-term and remains the cornerstone of ICP management. Intravenous mannitol is the most commonly used osmotic agent because of its easy availability and frequent usage by physicians.[5] It begins to exert its osmotic effect within 15–30 minutes of infusion, drawing water away from the interstitial spaces and into the intravascular compartment across the blood brain barrier, thus reducing the water content of edematous brain tissue. A 20% solution of mannitol is usually given in a dose of 0.25–1 gm/kg every 6 hours. Its beneficial effect lasts 4–6 hours. It is

preferable to give it through a central line as extravasation of the fluid causes thrombophlebitis. Serum osmolality is monitored regularly. It must be kept less than 320 mOsm/L to avoid renal complications. Mannitol is also a potent diuretic agent, so care must be taken to avoid dehydration and maintain euvolemia with isotonic fluids like normal saline (310 mOsm/L). Adverse effects include renal toxicity, dehydration, hyperosmolality and hypernatremia. Its prolonged use may cause rebound cerebral edema, so it is usually not given for more than 3 days. It should also not be used in the presence of hypovolemia, renal insufficiency and heart failure.

Hypertonic saline is also effective in lowering ICP. In addition to reducing the brain volume by creating an osmotic gradient, HTS also expands intravascular volume and increases cardiac output without significant nephrotoxicity or diuretic effect.[6] It can be administered as a continuous infusion with 3% solution at a rate of 10–40 mL/hour or as a bolus with either 3% solution or 23.4% solution. The aim is to increase sodium concentration to a range of 145–155 mEq/L and keep serum osmolality of 320 mOsm/L. This level is maintained for 48–72 hours. HTS is given through a central venous catheter to prevent phlebitis. It causes a rapid reduction of ICP and its duration of benefit may be significantly longer than mannitol. Unlike mannitol, repeated HTS administration does not diminish the ICP-lowering effect. It is preferred in hypovolemic and hypotensive patients during initial resuscitation, as intravascular volume can be increased while reducing ICP. It can also be used in renal insufficiency and can be interchanged with mannitol when the serum osmolality exceeds the limit. This ensures continued osmotherapy while the kidneys try to clear mannitol from the circulation. HTS can cause metabolic acidosis and electrolyte disturbance. It should be tapered slowly after prolonged use to prevent rebound edema. Its use in intracerebral hemorrhage to reduce ICP remains to be clarified.

Diuretics like frusemide help to improve water clearance. The aim is to produce hyperosmolarity without depleting intravascular volume. Free water loss is replaced with isotonic solutions like normal saline. The effect of a diuretic can last up to 2 weeks as tolerance to it does not occur.

Steroids

Steroids are used to reduce the cerebral edema surrounding tumors, abscess and other mass lesions. Intravenous dexamethasone is given in a dose of 4–8 mg every 6–8 hours. Their efficacy in acute strokes and head injury has not been established. In fact, they have a deleterious effect and are not recommended in the treatment of head injury.

Cerebrospinal Fluid Drainage

Cerebrospinal fluid drainage is the treatment of choice when raised ICP is due to increased CSF volume as in hydrocephalus from SAH or IVH. This can be done by an EVD, lumbar drain or serial lumbar punctures. If an EVD is already in place for ICP monitoring, it can be used to release CSF in small volumes of 3–5 mL at a time, when the ICP is high. This results in an immediate reduction of ICP. Continuous slow CSF drainage can also be instituted. CSF drainage is most useful for brief periods to reduce the ICP during plateau waves. Its long-term benefits are unclear. Keeping the EVD in situ for more than 5 days also increases the risk of infection in the ventricles.

Sedatives, Analgesics and Neuromuscular Blocking Drugs

Sedatives like midazolam, analgesics like fentanyl and non-depolarizing neuromuscular blocking drugs like vecuroneum help to reduce ICP. They are used in ventilated patients to avoid surges in ICP during suctioning, coughing, chest physiotherapy and positioning. They are given as a bolus followed by slow infusion. Propofol can be used as a substitute to vecuroneum. Simultaneous fentanyl and midazolam infusions are a common practice followed in many critical care units. Muscle relaxants do not alter the pupillary reflex, but other brainstem reflexes are affected. Their effects can be reversed in a matter of minutes if neurological evaluation is essential, and their use is more often beneficial than detrimental. Prolonged use of these drugs, however, increases the risk of critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) and predisposes to sepsis and deep vein thrombosis (Box 1).

REFRACTORY INTRACRANIAL HYPERTENSION

Decompressive Craniectomy

Urgent decompressive craniectomy (DC) is considered if the patient is deteriorating rapidly or if the ICP continues to rise despite medical management. It involves surgical removal of a large part of the skull bone with a duroplasty. This allows more room for the damaged edematous brain to expand. It results in an immediate drop in ICP and can be life-saving.[7] It may be performed early at the time of definitive surgery (for example, evacuation of subdural hematoma) or later, as a salvage procedure after medical management has failed. It is indicated in malignant middle cerebral artery (MCA) infarcts, large intracerebral hemorrhage, cerebellar hematoma or severe head trauma. It is usually performed unilaterally on the ipsilateral side of the lesion. A bifrontal craniectomy is performed in severe head injury patients with significantly elevated ICP when CT scan does not reveal a discernible lesion. Early decompressive surgery is also considered in situations where persisting with medical therapy results in loss of crucial time that could be used to salvage brain tissue at risk, if surgery is done promptly.

Pharmacological Barbiturate Coma

In intractable raised ICP refractory to all other medical and surgical therapies, high-dose barbiturate coma with pentobarbital or thiopental is induced. Barbiturate coma

Box 1: Management of raised intracranial pressure

- Urgent surgical evacuation of intracranial mass lesions, e.g. subdural/extradural hematoma or tumor, if detected on CT/MRI scan
- General measures—
  - Avoid hypoglycemia or hyperglycemia
  - Treat hyponatremia, if present
  - Maintain normal body temperature
  - Prompt treatment of seizures
- Specific measures—
  - Head position—keep head elevated at 30° to the horizontal
  - Blood pressure—
    - Maintain euvolemic state
    - Fluid correction with 0.9% normal saline or albumin
    - Vasopressor/inotropic agents if hypotension persists
  - Mechanical ventilation—
    - Effective but short lasting
    - Maintain PaCO2 at 30–35 mm Hg
  - Hyperosmolar therapy—
    - IV mannitol 0.25–1 g/kg every 6–8 hours
    - Hypertonic saline—IV 3% solution—bolus or infusion at 10–40 mL/hour
    - Diuretics—frusemide
  - Steroids—
    - IV dexamethasone—only for brain tumors and other mass lesions
  - CSF drainage—
    - In hydrocephalus (subarachnoid or intraventricular bleed) through EVD or lumbar drain or serial LPs
    - Later, if required: VP shunt
  - Sedatives, analgesics & neuromuscular blocking drugs—
    - Midazolam—sedative
    - Fentanyl—analgesic
    - Vecuronium or propofol—neuromuscular blocker
  - Refratory intracranial hypertension—
    - Decompressive craniectomy
    - Pharmacological barbiturate coma
    - Hypothermia

significantly reduces the cerebral metabolic rate, which in turn reduces CBF and CBV. This helps to reduce ICP.[1] Continuous EEG monitoring is required to maintain a burst suppression pattern. Burst suppression is an EEG pattern of alternating periods of high amplitude slow waves with periods of flat EEG and indicates adequate metabolic suppression. Thiopental was found more effective than pentobarbital in controlling refractory ICH in one study.[8] This therapy, however, is associated with the risk of major complications like severe hypotension, bronchopulmonary infection, respiratory failure, liver disturbance and disseminated intravascular coagulation. To avoid these, the minimal effective dose is given. Hypotension is aggravated by mannitol-induced dehydration and decreased cardiac filling secondary to mechanical ventilation. Vasopressor support, usually with norepinephrine is required to manage hypotension. Propofol has been used as a substitute for pentobarbital because of its reduced side effects.

Hypothermia

Hypothermia is also used to reduce refractory intractable ICH. The ICP-lowering effect is mainly due to reduction of cerebral metabolic rate. At about 30°C, cerebral metabolism reduces by 50%. Cooling to 32–36°C is attempted in patients with severe elevated ICP. Systemic hypothermia involves surface cooling by endovascular catheters or gastric lavage. Selective hypothermia involves a cooling cap or band. A greater benefit appears to accrue when the temperature is brought down to 32–34°C and when target temperature is maintained for more than 48 hours.[9] Improved outcomes in patients with severe head injury have also been recently reported with induced normothermia (36–36.5°C) which reduced fever burden and attenuated intracranial hypertension.[10] However, these benefits may be offset by serious adverse effects which include pneumonia, sepsis and cardiac arrhythmias. After the period of hypothermia, rewarming must be done slowly to avoid a rebound increase in ICP.

Hydrocephalus

Cerebrospinal fluid diversion is the treatment of choice in raised ICP due to hydrocephalus. An external ventricular drain (EVD) placed into the ventricles of the brain and connected to an external drainage system is effective in draining CSF and reducing ICP. A ventriculoperitoneal (VP) shunt cannot be performed immediately when hydrocephalus complicates meningitis or intraventricular hemorrhage as the tube would either get infected or blocked. EVD buys time. If hydrocephalus subsides, it is removed, but if it persists, then a permanent VP shunt is inserted. Endoscopic third ventriculostomy involves fenestration of the floor of the third ventricle under endoscopic vision. This fenestration enables communication between the third ventricle and the prepontine cistern.[11]

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B. Traumatic Brain Injury

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INTRODUCTION

Traumatic brain injury (TBI) is a serious public health problem worldwide. Although it affects people of all ages, there is a disproportionately large representation of young adults and children (maximum peak of 15–24 years). These individuals are premorbidly healthy and in the prime of their lives. So the impact on society, especially in terms of productivity, is profound. This more than justifies the large resource outlay for treating and rehabilitating these people. Although TBI is maximally seen in the young, it is the elderly who have the worse outcome. A large number of patients have polytrauma. The recognition and timely management of polytrauma has a positive impact on the outcome of head injury.

COMMON CAUSES

Motor vehicle accidents are the most frequent cause of TBI in young people, comprising about 50% of all TBI cases. Sports injuries, assaults, bullet injuries and occupational injuries are also commonly seen among children and young adults. Among penetrating injuries, gunshot wounds are the most lethal, with a 90% mortality. Blast injuries are commonly encountered during war and terrorist attacks. In contrast, falls are the commonest cause in elderly subjects over 65 years of age.

MECHANISMS OF INJURY

Traumatic brain injury can be either primary or secondary. Primary injury occurs at the time of impact and is the direct immediate result of the trauma. Blunt contact force is the most common mechanism of injury. Examples of blunt force are a direct blow or fall from a height or striking the windshield in a car crash. Forces of acceleration followed by sudden deceleration result in coup and contrecoup injuries. Coup injury is the direct injury to underlying tissue. It results in skull fracture, contusion, subdural/extradural hemorrhage and arterial dissection. Contrecoup is the second injury which occurs diagonally opposite the site of impact. The sudden acceleration-deceleration causes the brain to move relative to the skull along a linear axis till it strikes the skull on the opposite side. Contrecoup injury causes contusions and subdural hemorrhage. A fall on the occiput, for instance, will cause a contusion in the frontal lobe. Rotational acceleration causes the brain to move relative to the skull along a non-linear axis. It produces injuries ranging from mild concussion to severe diffuse axonal injury (DAI).

Secondary injuries are those that occur hours to days after the initial impact. Mortality and morbidity from secondary injury may exceed that of primary injury. Cerebral edema (perilesional or diffuse), hypotension, hypoxia, fever and raised intracranial pressure (ICP), all contribute to secondary brain injury. At the cellular level, damage to neurons occurs in two ways: (1) excitotoxicity and (2) apoptosis. In excitotoxicity, release of excess amounts of excitatory amino acids like glutamate results in increased activation of proteases and lipases, calcium channel mediated neuronal injury and cell death. Apoptosis is programmed cell death with DNA fragmentation which is triggered by tumor necrosis factor.

CLINICAL ASSESSMENT

Despite its drawbacks, the Glasgow Coma Scale (GCS) still remains the gold standard and the most universally utilized scale for assessing the severity of TBI. The best eye-opening response, verbal and best motor responses are graded, noting asymmetric responses in the latter. Head injury with GCS of 13–15 is considered mild, 9–12 is classified moderate, while a score of 3–8 qualifies as severe head injury. Some pitfalls and fallacies of the GCS need a mention. Firstly, assessment is difficult if the patient has been sedated in the ambulance. Then again, an intubated patient is unable to give a verbal response. This has led to greater weightage being given to motor responses in particular. The GCS is also not powered to detect focal neurological deficits which are seen with structural mass lesions.

Traumatic brain injury rarely occurs in isolation. Most patients have polytrauma with extracranial injury seen in 35% of cases. An early thoracoabdominal assessment is essential. Fractures of long bones and any visceral injury to the abdomen must be looked into. About 6% of patients with severe TBI also have cervical spine injury. The neck must be most gently handled and preferably immobilized so as not to worsen associated cervical cord trauma. Signs of myelopathy like paraplegia, quadriplegia, impaired sensation below a level on the trunk and sphincter disturbance must be looked for.

Fractures of the skull base are often difficult to visualize on X-ray or CT scan. They carry an increased risk of meningitis due to breach of the dura mater. The diagnosis is often made on clinical signs. Suspected anterior cranial fossa fractures present with raccoon eyes—bilateral periorbital ecchymosis, anosmia due to olfactory apparatus damage and CSF rhinorrhea. The latter occurs in 25% of patients with anterior skull base fracture and cribriform plate injury. It is often self-limiting. Measures like elevation of the head end of bed and CSF aspiration/drainage are beneficial. In suspected middle fossa and temporal bone fracture, the battle sign is seen. It is an area of ecchymosis over the mastoid process behind the ear and may appear 24 hours after injury. CSF leak through the ear (CSF otorrhea) indicates rupture of tympanic membrane. A pulsating exophthalmos with a retro-orbital bruit points to a carotid-cavernous fistula.[1] Involvement of cranial nerves III, IV and VI is seen in orbital fracture and cavernous sinus injury.

Ipsilateral 7th and 8th nerve palsies occur with fracture of the petrous part of the temporal bone. A clivus fracture causes an isolated VIIth nerve palsy.

The pupillary light reflex gives valuable information. Bilateral impairment may indicate a brainstem lesion. Unilateral impairment signifies optic or oculomotor nerve lesion, which can be further differentiated by comparing the consensual and direct responses. Clinical evidence of a focal neurological deficit must be carefully sought. A drowsy, confused patient with gaze preference to one side and contralateral hemiparesis must be urgently investigated for an extracerebral hematoma. Neurological evaluation must be repeated at frequent intervals. Deterioration in TBI patients can be rapid and early signs of impending herniation must not be missed. In a comatose patient, a pupil, which starts dilating or a change in upper limb motor response from withdrawal to an extensor thrust on noxious stimulus, is an early sign of impending herniation.

NEUROIMAGING

Computed tomography scan of the head is the cornerstone of diagnosis and management of TBI. It is quick to perform and sensitive in detecting cerebral contusions, skull fractures, extracranial hematomas, subarachnoid hemorrhage (SAH) and cerebral edema with midline shift. However, it is not sensitive enough to detect abnormalities in DAI. A CT angiography (CTA) may be performed if an arterial dissection is suspected, especially if associated cervical spine injury exists. Serial CT scans are performed, depending on the patient's neurological status and to monitor the size of contusions and other bleeds, if present. About 1 in 6 patients with DAI will develop a new focal lesion on repeat CT.[2]

A magnetic resonance imaging (MRI) scan provides a vastly superior structural assessment of parenchymal brain insult, especially of the brainstem and craniovertebral junction. It detects microhemorrhages and other lesions associated with DAI. The disadvantage of MRI is that it takes longer to perform and may be risky in the initial stage when the patient is unconscious and hemodynamically unstable. Diffusion tensor imaging (DTI) is a new MRI modality which highlights the integrity and connectivity of axons.[3] It is more sensitive than conventional MRI for detecting DAI.

INTRACRANIAL INJURIES IN MODERATE TO SEVERE TBI

Cerebral Contusion

It is a bruising of the brain caused by coup and contrecoup injury. Contusions are commonly seen in the orbitofrontal and anterior temporal lobes. On a CT scan, they appear as areas of edema with foci of hemorrhage within. About 50% of them expand in the first 24–48 hours, causing increased mass effect, worsening GCS score and raised ICP. Patients on antiplatelet or antithrombotic drugs have a high risk of contusion expansion (Fig. 2).[4]

Subdural Hematoma

Acute subdural hematoma (SDH) is the most common traumatic hematoma, occurring in 35–40% of patients with severe TBI. It is a collection of venous blood between the dura and arachnoid mater. The shearing force generated by trauma causes the bridging veins between the surface of the brain and the dural sinus to tear. SDH is more likely to occur with falls than with motor vehicle accidents because acceleration-deceleration is more rapid in falls. Patients usually present with acute headache, vomiting, drowsiness, confusion and hemiparesis. CT scan shows the hyperdense crescentic-shaped blood collection in the frontoparietal subdural space. Large SDHs cause midline shift and ipsilateral ventricular compression. Thin ones may be asymptomatic and detected incidentally on CT scan (Fig. 3).

Extradural Hematoma

Extradural hematoma (EDH) is a convex collection of blood between the skull and the dura. It is seen in 1–10% of TBI and is caused by a temporal bone fracture which tears the middle meningeal artery. EDH is mainly temporal in location because the temporal bone is thinner than the rest of the skull and breaks easily, lacerating the middle meningeal artery. MVA and falls account for the majority of cases. The characteristic clinical picture is termed "talk and die". The patient wakes up after an initial period of unconsciousness. This is the lucid interval, but it is soon followed by rapid deterioration with unconsciousness. Some patients with small EDH remain neurologically intact with minimal deficits (Fig. 4).

Subarachnoid Hemorrhage

Subarachnoid hemorrhage is usually associated with contusions or SDH. The differentiation between traumatic and aneurysmal SAH may sometimes be difficult, especially if a clear history of trauma is lacking. Typically, subarachnoid blood in TBI is superficially seen over the cortex and not in the basal cisterns as in aneurysmal bleed. However, if there is a doubt, it is best to do a CTA or a digital subtraction angiography. Traumatic SAH also produces delayed vasospasm with ischemic deficit, but less than with aneurysmal SAH and is also unlikely to rebleed.

Diffuse Axonal Injury

Patients with DAI caused by severe TBI are usually comatose with pupillary asymmetry and decorticate/decerebrate posturing. CT scan of head does not reveal any obvious hemorrhage or edema. Severe deceleration and rotational forces cause widespread shearing of axons located in the deep white matter. Axolemmal disruption and axonal retraction result, which finally lead to Wallerian degeneration. MRI of brain detects small punctate hemorrhages on gradient echo sequences in corona radiata, gray-white interfaces, corpus callosum (especially splenium), midbrain and pons. Corpus callosal lesions are typically seen in this type of injury.

DAI carries a high mortality of 50% and is a common cause of persistent vegetative state. Recovery may take months to years (Fig. 5).

PREHOSPITAL EMERGENCY MANAGEMENT OF MODERATE TO SEVERE TBI

Time is a vital factor in treating moderate to severe TBI. Early and appropriate interventions help to limit or prevent secondary brain injury. Emergency management of TBI commences when medical personnel reach the trauma victim and continues all the way through ambulance transport to the hospital. Every effort should be made to ensure that the patient reaches the hospital intensive care unit (ICU) in the shortest possible time. Rapid trauma-to-hospital time and transfer to a neurotrauma center reduce mortality.[5] All precautions, especially neck immobilization, must be taken whenever the patient is moved.

Airway, breathing and circulation are priority issues to be addressed during transport. The airway can be obstructed by foreign objects like dentures or accumulation of blood, secretions and vomit. Direct pharyngeal trauma may also cause airway collapse. If pharyngeal suction is unable to clear the airway, a tracheal intubation must be done. Massive facial trauma or a significant upper airway swelling may sometimes necessitate an urgent direct tracheotomy or cricothyroidotomy which could be life-saving. The arterial oxygen tension (PaO_2) must be monitored with a pulse oximeter. Breathing may be compromised by rib fractures causing a flail chest, pulmonary contusions or hemopneumothorax. Diaphragmatic injury,

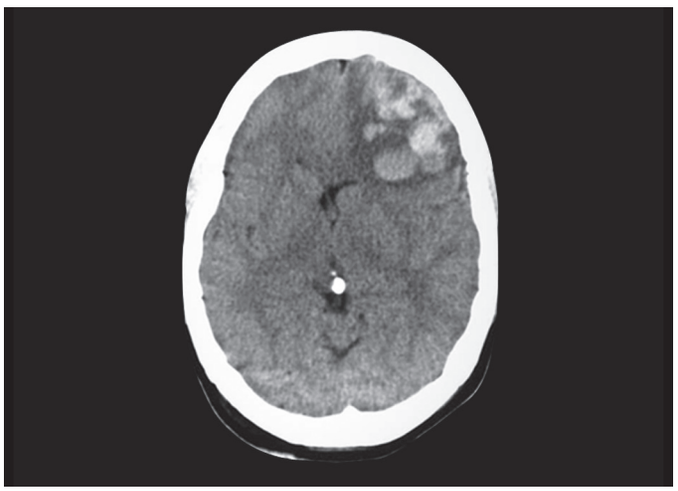

Fig. 2: Hemorrhagic contusions: CT scan reveals multiple focal areas of hemorrhage in left frontal region with mass effect on left lateral ventricle

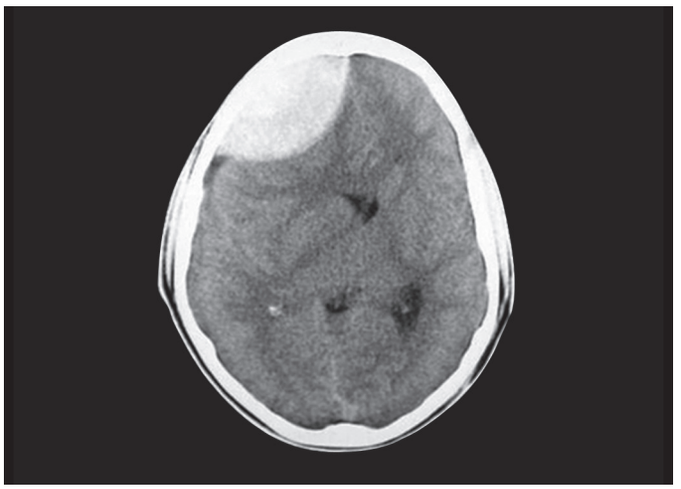

Fig.4: Extradural hematoma: CT scan reveals a large biconvex hyperdense lesion in the right frontal region causing significant mass effect representing an extradural hematoma

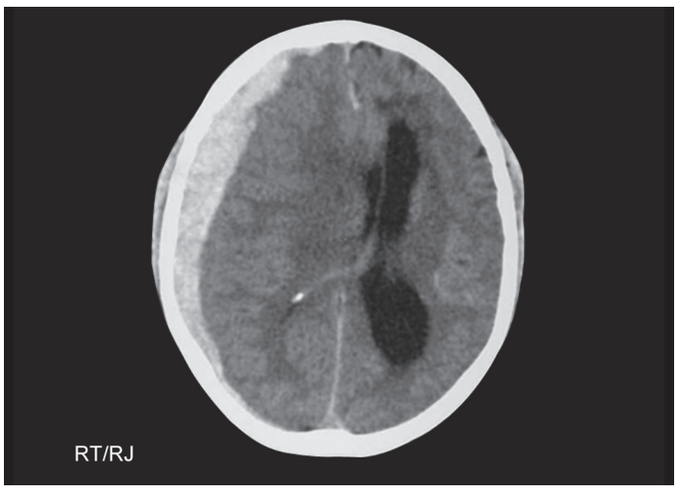

Fig. 3: Subdural hematoma: CT demonstrates a large concavoconvex hyperdensity representing a subdural hematoma causing mass effect on the right lateral ventricle and a consequent shift of the midline structures to the left

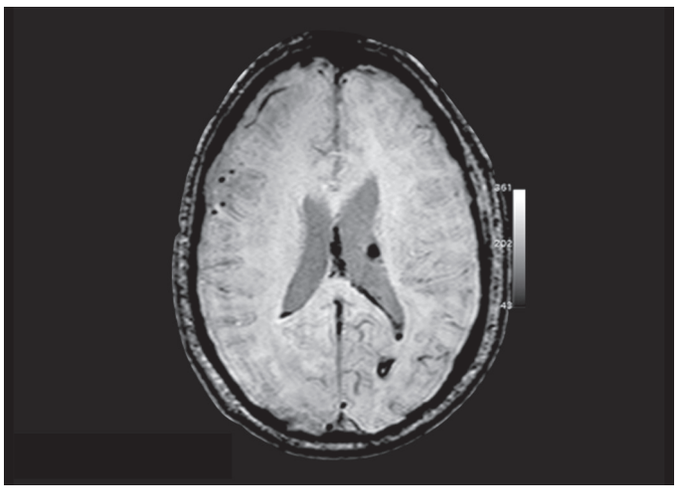

Fig. 5: Diffuse axonal injury: MRI SWI images demonstrate small SWI hypointensity representing microhemorrhages due to diffuse axonal injury

phrenic nerve paralysis due to spinal cord injury and respiratory center involvement by brainstem injury are other causes of respiratory distress. Supplemental oxygen is given through a face mask, but if the situation warrants, Ambu bag ventilation through a face mask or an endotracheal tube is instituted. Prophylactic hyperventilation is strictly avoided in the prehospital setting as it worsens tissue hypoxia and aggravates secondary brain injury.

Hypotension (systolic blood pressure <90 mm Hg) can occur due to significant scalp bleeding, internal hemorrhage or an acute abdomen. Scalp lacerations tend to bleed profusely due to a combination of rich scalp blood supply and their poor vasoconstrictive ability. It is difficult to give whole blood or packed cells in the ambulance. The only recourse is to treat the hypovolemic shock aggressively with intravenous fluids. Crystalloids (saline fluids) are preferred to colloids (albumin).[6]

ICU Management of Severe TBI

Head Posture

Patients are usually nursed in the supine position with the head elevated at about 30° to the horizontal. The neck should not be twisted and tapes around the neck avoided. These measures ensure adequate jugular venous return from the brain.

Airway and Oxygenation

Hypoxia at the time of admission is associated with a worse outcome.[7] A PaO_2 of 80–120 mm Hg, $PaCO_2$ of 35–40 mm Hg and arterial oxygen saturation more than 90% should be maintained. Indications for intubation and ventilation include a GCS score less than 9 (without sedation), declining oxygen saturation of less than 90%, signs of respiratory distress, rising $PaCO_2$ levels more than 45 mm Hg in patients without chronic obstructive pulmonary disease, copious secretions which are difficult to clear and aggressive, hyperexcitable patients who require sedation.

Blood Pressure

Systolic BP must not be allowed to fall below 90 mm Hg. The mean arterial pressure should be maintained above 70 mm Hg with CVP more than 5 mm Hg. Judicious use of fluids (saline or albumin) ± pressors help to stabilize BP. Whole blood or packed cells can be given if significant blood loss has occurred. If BP is elevated, it is wise not to acutely lower it unless systolic BP rises above 180 mm Hg. Vasodilators like sodium nitroprusside and hydralazine are avoided as they may increase ICP.

Sedatives and Analgesics

Patients with severe TBI are often extremely restless and agitated. Their breathing may not be synchronized with the ventilator settings. Coughing, repeated endotracheal suction and frequent change of body position, all result in spurts of hypertension and raised ICP. Judicious use of sedatives and analgesics help to control ICP by blunting the above effects. Intravenous propofol and fentanyl are commonly used. Propofol is the preferred sedative because of its rapid onset and short half life. It is given as an infusion at a rate of 0.1–5 mg/kg per hour. Long-term infusions are best avoided in children because of a high risk of propofol infusion syndrome (mentioned in subchapter Status Epilepticus of Chapter Neurological Problems) and hepatic disturbance. Midazolam or lorazepam can be used as an alternative to propofol. The above drugs also have antiepileptic efficacy. Dexmedetomidine hydrochloride is a new agent that has rapid on-off properties and causes little respiratory depression. It is suitable for procedural uses and for ventilator weaning and extubation.[8] Fentanyl is the commonly used analgesic in severe TBI. It has a rapid onset, quick clearance and a short-lived effect, which permit frequent neurological assessments. It may cause respiratory depression, hypotension and vomiting.

Seizure Prophylaxis

In a population-based study of seizures after TBI, 17% of patients developed seizures in the first 7 days after injury, with nearly half of them occurring in the first 24 hours.[9] Seizures in this setting can acutely increase cerebral metabolism and ICP with disastrous consequences. So, current guidelines suggest that prophylactic antiepileptic drugs (AEDs) be given to prevent early post-traumatic seizures in the first 7 days. They are not, however, indicated to prevent long-term seizures.[10] Phenytoin/fosphenytoin or levetiracetam are commonly used AEDs. Levetiracetam is being used more frequently due to its favorable side effect profile. In the paralyzed and ventilated patient, electroencephalographic (EEG) monitoring helps to detect seizures which may be masked by sedatives and muscle relaxants.

Temperature and Blood Sugar

Fever is associated with elevated ICP, more severe neurological impairment and a longer ICU stay. Hence, infections (commonly respiratory and urinary tract) must be treated adequately with appropriate antibiotics and body temperature maintained below 38°C. Prophylactic antibiotics are used prior to procedures like intubation to reduce the risk of pneumonia. Most CSF leaks resolve spontaneously in a few days; hence, prophylactic antibiotics in this setting are not recommended because of the risk of drug resistance. Blood sugar should also be maintained in the normal range. Neither hyperglycemia nor hypoglycemia is desirable. No clear outcome benefit has been reported with intensive insulin therapy.[11]

Steroids

The use of corticosteroids is contraindicated in TBI patients (Level 1 evidence). The multicenter, randomized CRASH (corticosteroid randomization after significant head injury) trial showed that the risk of death was, in fact, higher in the steroid group compared to placebo patients.[12]

Intracranial Pressure Monitoring

Intracranial pressure monitoring has been associated with better outcomes in severe TBI. It is indicated in TBI patients having GCS of 8 or less with an abnormal CT scan showing contusion, hematoma or swelling or with normal CT scan if they have two or more of the following: age over 40 years, unilateral or bilateral motor posturing or systolic BP less than 90 mm Hg.[13] An external ventricular device is the gold standard of ICP monitoring as it serves the dual purpose of measuring ICP and draining CSF as required. It is advantageous to monitor ICP for at least 3 days post-injury to cover the expected period of occurrence of cerebral edema. ICP monitoring should continue for as long as raised ICP persists and can be discontinued after 48 hours of normal pressure trace (for more details on ICP monitoring, please refer to the subchapter Raised Intracranial Pressure of Chapter Neurological Problems).

Management of Raised ICP

The frequency of raised ICP is as much as 80% in comatose, head injured patients and is a strong independent predictor of mortality and morbidity. Hence, effective management of raised ICP holds the key to a favorable outcome. The goal of ICP management is to keep ICP less than 20 mm Hg. Cerebral perfusion pressure (CPP) of more than 60 mm Hg is recommended unless there is evidence of cerebral hypoperfusion, in which case a higher CPP is necessary. However, a CPP more than 70 mm Hg increases the risk of acute respiratory distress syndrome 5 times.[14] Moderate increase of ICP up to even 30 mm Hg may be tolerated, so long as arterial pressure maintains CPP at more than 60 mm Hg.

If ICP rises, simple extracranial causes must first be ruled out. Is the airway obstructed? Is the effect of sedatives wearing off and leading to the person bucking the ventilator? Is there an elevation of arterial $PaCO_2$ or a fall of PaO_2? Is there fever or occult seizure activity? Dilutional hyponatremia due to free-water overloading can also cause cerebral edema and rise in ICP. Correction of the above disturbances, if present, would have a beneficial effect.

Ideally, treatment should focus on the main cause of raised ICP. If an increase in cerebral blood volume is the predominant factor responsible, then hyperventilation is the most suitable therapy. An increase in brain water content (cerebral edema) is best treated by osmotherapy, while increased CSF outflow resistance responds to CSF drainage. Therapy for raised ICP is described in detail in the subchapter Raised Intracranial Pressure of Chapter Neurological Problems.

Surgical Considerations

Traumatic brain injury patients with acute SDH or EDH need urgent surgical evacuation if their GCS score is less than 9, volume of hematoma is more than 30 mL or midline shift is more than 5 mm on CT scan. Pupillary inequality and a fall in GCS score by 2 or more points from the time of trauma to the time of examination also warrant emergency surgery. A cautious wait-and-watch approach is adopted if the patient has a relatively preserved sensorium with a GCS of 9 or more and if the SDH or EDH bleed is small (<30 mL) with a midline shift of less than 5 mm. These patients need close monitoring, both clinically and with follow-up CT scans.[15]

The role of early surgical evacuation of intraparenchymal hematomas and hemorrhagic contusions is debatable. The increasing trend is to manage these patients conservatively at first, keeping a close watch on the level of arousal along with continuous arterial and ICP monitoring. Deterioration of these parameters and an increased mass effect on repeat CT scan should then prompt surgical evacuation. A neurosurgical consultation should be obtained earlier rather than later. Early surgical intervention is also indicated for compound depressed skull fractures, about half of whom have an associated dural tear. Debridement, removal of contaminant materials and secure wound closure should be carried out as early as possible.

Decompressive craniectomy is considered in refractory cases of raised ICP when medical management fails. It involves removing a large portion of the skull in absence of a large mass-occupying lesion like SDH or EDH. The aim of surgical decompression is to provide room for the injured brain to expand in order to preserve the deep vital parts of the brain. Decompression may be performed on one side of the skull if there is ipsilateral pathology. A bifrontal craniectomy is done if CT scan does not reveal a discernible lesion. Although ICP is reduced in most patients, the effect on outcome remains to be clarified.

Emerging Concepts—Multimodal Monitoring

Intracranial pressure measurement only gives indirect information about brain tissue oxygenation, cerebral metabolic activity and cerebral blood flow (CBF). Multimodal monitoring enables direct monitoring of these variables and can usefully complement ICP monitoring in the management of severe TBI. The various components of multimodal monitoring include partial brain tissue oxygen tension ($PbtO_2$), CBF, cerebral microdialysis, bispectral index and jugular venous oximetry.

Direct measurement of $PbtO_2$ detects compromise of oxygen delivery to brain tissue earlier than ICP monitoring. In this method, cerebral oxygen sensor probes are inserted into an area of suspected compromise in the brain parenchyma. They can detect focal ischemia which may otherwise have gone unnoticed.[16] Regional CBF can be measured either directly with thermal diffusion probes or indirectly with transcranial Doppler ultrasound which measures blood velocities in intracranial vessels. Jugular venous oxygen saturation is also an indirect means of measuring/monitoring CBF. It is estimated with the help of a fiber-optic catheter inserted through the internal jugular vein into the jugular bulb at the skull base. Low values indicate reduced CBF and impending ischemia. Cerebral microdialysis assesses the metabolic status of the brain. A small catheter placed in the

brain parenchyma measures extracellular levels of glucose, lactate, pyruvate, glutamate and glycerol. It is used as a marker for cellular distress.[17] Microdialysis analysis has shown that very tight systemic glucose control with insulin, in fact, results in an unfavorable pyruvate/lactate ratio and increased mortality.[18] These new modalities and devices, however, have their limitations and doubts have been raised on their efficacy. Large controlled trials addressing their safety and efficacy in severe TBI are required before they can be recommended for routine use in ICUs.

Prognosis of Severe TBI

Severe TBI is associated with a 30% mortality. A further 16% of patients are disabled with severe neurologic deficits. Age, GCS score, pupillary response, hypoxia and hypotension are prognostic factors shown to correlate with outcome.[19] A midline shift of more than 5 mm on initial CT scan and compression of mesencephalic cistern are associated with high mortality. Patients with DAI usually have a poorer outcome than other forms of TBI. However, DTI studies do show restoration of axonal integrity in the long term. Comprehensive neurorehabilitation improves functional outcome, with 85% of recovery occurring in the first 6 months.[20]

Rapid progress in neuroimaging and neurocritical care over the last few years has resulted in improved outcomes of TBI patients. Today, TBI is the subject of active clinical research both on the pharmacological and surgical fronts. Biomarkers of brain injury and genetic testing will play an important role in guiding specific therapies in the future. Present TBI treatment protocols have resulted in some remarkable recoveries, making all the effort put in seem worthwhile.

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C. STROKE

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INTRODUCTION

Of all the neurological emergencies, stroke is probably the best known and most feared by physicians and the general public alike. It is a leading cause of mortality and morbidity all over the world with an estimated 22 million people falling victim to it each year.[1] While a large ischemic stroke carries a mortality of about 15%, the figure rises to nearly 50% for a major intracerebral hemorrhage (ICH). Raised intracranial pressure (ICP) is the most common cause of death in all types of stroke. Other causes include aspiration pneumonia, pulmonary embolism and cardiac arrhythmias. Strokes can be broadly classified into two groups—(1) ischemic stroke caused by occlusion of a blood vessel with a resultant infarct (80% of strokes) and (2) hemorrhagic stroke due to rupture of a vessel with bleeding within the brain (20% of strokes).

ACUTE ISCHEMIC STROKE

Acute ischemic stroke (AIS) is usually caused by one of the following mechanisms—

- *Large vessel atherothrombosis* Atherosclerotic occlusion of a large extra/intracranial artery occurs either by an in situ thrombus or by dislodgment of an embolic fragment with distal arterial block (artery-to-artery embolism).
- *Cardioembolism* The heart is an important cause of embolic strokes. Multiple infarcts at different times in different vascular territories raise the possibility of a cardiac source of embolus. Atrial fibrillation (AF) with or without valvular disease is probably the most common cause. If AF is associated with congestive heart failure, low ejection fraction or ischemic heart disease, the risk is particularly high. Acute myocardial infarct (especially anterior wall), left ventricular (LV) thrombus, prosthetic valves, cardiomyopathy and infective endocarditis are other common causes. In a patient with multiple strokes where no cause is detected, it would be prudent to do a 24- or 48-hour Holter monitoring to detect any intermittent episodes of AF.
- *Small vessel disease* A microangiopathy affecting small penetrating arteries (50–200 μ in diameter) causes small subcortical infarcts called lacunes. Hypertension and diabetes are the most important causes. Lipohyalinosis is the underlying pathological process, although atherosclerosis is also responsible in some cases.

Other less common but important causes of AIS need a mention. Young stroke patients presenting with severe neck pain and a prior history of sudden jerking or trauma to the neck are likely to have an arterial dissection. Carotid artery dissection is associated with pain in the anterior part of the neck, while in vertebral artery dissection, the pain occurs more posteriorly. Stroke in young patients with multisystem involvement should raise the suspicion of systemic lupus erythematosis. Stroke usually occurs during the course of the illness, though sometimes it is the presenting feature. A delayed diagnosis of tuberculous meningitis can result in disabling strokes due to thick basal exudates constricting the intracranial vessels. Hematological disorders like polycythemia, thrombocytosis and leukemia can also underlie strokes.

PATHOPHYSIOLOGY OF ACUTE CEREBRAL ISCHEMIA

Occlusion or stenosis of a blood vessel impairs the blood supply to the brain tissue perfused by that vessel. The cerebral blood flow in a normal adult brain at rest is about 50–55 mL/100 g per minute. When it decreases to 18 mL/100 g per minute, a threshold of electrical failure occurs. Although neurons do not function normally at this level, they still have the potential to recover. When blood flow falls to 8 mL/100 g per minute, a threshold of membrane failure is reached, at which point neuronal cell death occurs. These thresholds represent the upper and lower limits of the ischemic penumbra, which represents damaged but potentially salvageable tissue. All attempts to re-establish blood flow are made to prevent this area from getting infarcted. This is the principle underlying the various reperfusion strategies employed in AIS management.

CLINICAL ASSESSMENT

The sudden onset of neurological symptoms points to a stroke, although other conditions mimicking stroke like acute demyelination, seizure, hypoglycemia and cerebral tumor must be excluded. Severe headache, vomiting and seizures at onset are uncommon in AIS and raise the possibility of ICH or subarachnoid hemorrhage (SAH). This distinction between an infarct and a hemorrhage is not always clear on clinical grounds. The precise time of onset of the stroke is essential to ascertain from the patient or a witness in order to plan the appropriate reperfusion strategy. If a patient wakes up from sleep with neurological symptoms, the time of onset is taken as the time he was last seen normal.

At the time of first patient contact, a quick, brief clinical and neurological examination is performed. Focal neurological deficits of stroke can be quickly assessed with the help of the National Institutes of Health Stroke Scale (NIHSS). It is a widely accepted standardized measure of the neurological deficit caused by AIS. It takes only a few minutes to perform and is used to assess the severity of a stroke. Low scores (<10) indicate a mild stroke with likelihood of a favorable outcome, while high scores (>20) indicate severe neurological deficits.[2]

DIAGNOSTIC EVALUATION

Computed tomography scan of the head is performed as soon as possible to rule out a cerebral hemorrhage. It may be normal in early AIS. Signs of a recent acute infarct on CT scan include loss of differentiation between the cortical gray and underlying white matter, sulcal effacement, swelling of cortical gyri and loss of insular ribbon. The hyperdense MCA sign on unenhanced CT scan indicates occlusion of the mainstem MCA. MRI is highly sensitive in detecting the presence and extent of an infarct. A bright signal on diffusion weighted image (DWI) with a corresponding dark signal on apparent diffusion coefficient (ADC) sequence indicates an acute infarct. Perfusion MRI/CT scans detect the presence of an ischemic penumbra representing potentially salvageable tissue. It appears as a region of low perfusion which is larger than the bright diffusion weighted region (infarct core). This is called the diffusion-perfusion mismatch. A large diffusion-perfusion mismatch indicates a large penumbra and tissue at risk and warrants a more intensive reperfusion strategy like intra-arterial thrombolysis (IAT). This mismatch is sometimes used as a criterion to select patients for intravenous thrombolysis (IVT) beyond the 3-hour window period, even up to 9 hours after stroke onset.[3] MR-Angiography (MRA) and CT-Angiography (CTA) help to visualize the entire cerebral vasculature from the aortic arch to the Sylvian branches. The degree of stenosis in extracranial and intracranial vessels is accurately determined by them. A digital subtraction angiogram (DSA) is not routinely performed except in suspected vasculitis, arterial dissection or significant carotid stenosis prior to endarterectomy.

A 2D echocardiogram (ECG) is ordered in AIS to check for a possible cardioembolic source. If it is strongly suspected and the 2D echocardiography is normal, a transesophageal ECG is done to look for abnormalities in the atrial appendage or thoracic aorta. A Holter monitor helps to detect intermittent cardiac arrhythmias. Basic hematological and biochemical tests which are carried out in all stroke patients include a complete hemogram, platelet count, prothrombin time (PTT), blood sugar, urea, creatinine, electrolytes and lipid profile. More detailed work-up is required in atypical and young strokes and those without the usual risk factors.

REPERFUSION STRATEGIES IN ACUTE ISCHEMIC STROKE

Time is the single most important factor in any strategy aimed at re-establishing blood flow in an occluded vessel. The window of opportunity for thrombolysis is small and every minute counts. In that sense, stroke management is a true emergency. Public awareness of common stroke symptoms must be created and a well-rehearsed plan put in place to ensure that stroke patients reach the hospital in the shortest possible time. Valuable time is often lost waiting for the family doctor to come home to examine the patient. The hospital must be fully geared to handle this emergency. Stroke units with involvement of the neurologist, physician, senior residents, nurses, neuroradiologist, neurosurgeon and pathologist have had a beneficial effect on outcomes. In centers lacking expertise, telemetric contact with tertiary specialist centers facilitates thrombolytic therapy and other treatment decisions.

Intravenous Thrombolysis

All patients presenting within 4.5 hours of an AIS should be considered for IVT with recombinant tPA (alteplase). The advantage of tPA over other thrombolytic agents is that it is clot specific because of its high affinity for plasminogen in the presence of fibrin. This allows efficient activation of plasminogen in the clot but very little activation in the plasma. Hence, the systemic effects are modest. The landmark National Institute of Neurological Disorders and Stroke (NINDS) trial demonstrated that AIS patients who received intravenous (IV) tPA within 3 hours of stroke onset had a more favorable outcome at 90 days than those who did not receive the drug.[4] Those who received alteplase within 90 minutes of stroke onset fared better than those who received it later than 90 minutes, emphasizing the importance of minimizing the door-to-needle time. The third European Cooperative Acute Stroke Study (ECASS III) showed that intravenous (IV) recombinant tissue plasminogen activator (rtPA) given 3–4.5 hours after onset of stroke symptoms also produced a modest but significant improvement in clinical outcome without increased risk of symptomatic ICH.[5] Results from the large, multicenter third international stroke trial (IST-3) suggest an extended benefit for IV rtPA up to 6 hours of stroke onset.[6] Most clinical trials for IVT enrolled patients less than 80 years of age. However, in the above-mentioned IST-3 trial, 53% of the enrolled patients were over 80 years and they also benefited from thrombolysis. Their risk of bleeding was no different from that of other age groups.[6]

Intravenous thrombolysis carries a significant risk of intracranial bleeding (6.4% in the NINDS trial).[4] However, the benefits of this therapy appear to outweigh the risks. A checklist of exclusion criteria for IVT exists in order to minimize the risk of bleeding and other adverse effects (Box 2). Notable contraindications to IVT include prior history of major surgery within the past 14 days, large cerebral infarct covering more than one-third of the vascular territory, prior ICH, history of gastrointestinal tract or urinary bleeding in the past 21 days, current oral anticoagulant therapy with international normalized ratio (INR) greater than 1.7 or heparin within 48 hours of presentation with prolonged activated PTT (aPTT), platelets less than100,000 and BP higher than 185/110 mm Hg. Patients with a mild deficit (NIHSS of 4 or less) and those who are spontaneously recovering are also not considered for IVT.

The dose of IV tPA is 0.9 mg/kg up to a maximum of 90 mg, with 10% of dose given as a bolus over 1 minute and the remaining 90% as an infusion over 1 hour. If BP is higher than 185/110 mm Hg, it has to be first reduced with IV labetalol (10–20 mg) before starting alteplase. It is preferable not to

Box 2: Indications and contraindications for intravenous thrombolysis

Indications—
- Acute ischemic stroke with significant neurological deficit [National Institutes of Health Stroke Scale (NIHSS ≥4)]
- Onset time within 4.5 hours
- Head computed tomography does not show hemorrhage or alternative diagnosis

Contraindications—
- Intracranial hemorrhage on CT or clinical suspicion of subarachnoid hemorrhage
- Mild or rapidly improving neurologic deficit
- Known CNS vascular malformation or tumor
- Major surgery in the past 14 days or minor surgery in the past 10 days
- Severe head trauma in the preceding 3 months
- Active internal bleeding within 21 days
- Arterial puncture at a noncompressible site within 7 days
- Patient on oral anticoagulant or use of heparin in the previous 48 hours
- PT-international normalized ratio (INR) greater than 1.7, PTT greater than 40 s, platelet count less than 100,000
- Systolic BP higher than 185 mm Hg or diastolic BP higher than 110 mm Hg
- Seizure at onset
- Blood sugar less than 50 mg% or greater than 400 mg%

insert a urinary catheter, nasogastric tube or a central line for the first 24 hours. Arterial puncture at noncompressible sites must also be avoided. BP is closely monitored every 15 minutes for 2 hours after starting the infusion, then every 30 minutes for 6 hours and then every hour up to 24 hours. No antiplatelet or antithrombotic drug is given for the first 24 hours. If the patient's sensorium or neurological deficit worsens, the infusion must be discontinued immediately and an urgent noncontrast CT scan of the head done to rule out an ICH or hemorrhagic transformation of the infarct.

Intravenous thrombolysis, as beneficial as it has been, is not without its limitations. It is not very effective in patients with severe stroke where the NIHSS score is 20 and above. Most of these patients have a large vessel occlusion (ICA, MCA, basilar artery). The recanalization rate for these occlusions with IVT is low (around 20%) compared to higher intra-arterial recanalization rates (60–70%).[7] Besides, a very small proportion of AIS patients receive IVT due to the short therapeutic window period and the presence of stringent exclusion criteria. Hence the need for other reperfusion strategies.

Intra-arterial Thrombolysis

For those patients who present beyond the window period for IVT and in whom a large penumbra (i.e. a large perfusion-diffusion mismatch on MRI) with occlusion of large extracranial or intracranial arteries (ICA, MCA or basilar artery) is observed, IAT with direct delivery of the lytic drug is considered. In this way, a high concentration of drug is delivered locally into the clot, resulting in increased recanalization rates with less bleeding and other systemic complications. IAT is also an option for those in whom IVT is contraindicated. The PROlyse in acute cerebral thromboembolism (PROACT–II) trial demonstrated benefit of intra-arterial prourokinase in the treatment of MCA occlusions within 6 hours of onset. A good outcome was observed in 40% of the prourokinase group versus 25% of the control patients. The recanalization rate was also higher in the treated group compared with the controls (66% vs 18%).[8] The window period for vertebrobasilar intervention has not been clearly defined. Intra-arterial urokinase and rtPA have been beneficial in treating basilar artery occlusions even beyond 12 hours after onset and, in some cases, more than 24 hours. This extension of the time window is based on the dismally poor natural history of severe brainstem stroke (>90% cumulative morbidity and mortality), whereas successful revascularization has the potential to significantly improve outcome. Intra-arterial urokinase administered to 106 patients with basilar artery occlusion resulted in recanalization in nearly 70% of patients, a moderate to good clinical outcome in 45% and a mortality of 41%.[9] Attempts have been made to combine IV rtPA with intra-arterial rtPA, the so-called "bridging therapy".[10] This therapy allows immediate access to IVT, but recognizes the fact that the low recanalization rate with IVT can be improved with the intra-arterial approach for large artery occlusion (MCA, ICA and basilar artery).

Mechanical Clot Retrieval Devices

Mechanical embolectomy devices like the mechanical embolus removal in cerebral ischemia (MERCI) device and penumbra device cause recanalization of the occluded vessel by mechanical removal of the clot.[11] They are used when thrombolytic therapy is contraindicated or when it has failed to cause recanalization. The therapeutic window for intervention with these devices is 8 hours from stroke onset. These two devices have got FDA approval on the basis of improved recanalization rates rather than improved stroke outcomes. The penumbra trial showed that the device is safe and effective in recanalizing occluded vessels but its impact on clinical outcome was unclear.[12] These devices are operator-dependent and good outcomes depend on the skill and experience of the interventionalist.

Stent Retrievers

Stent retrievers are combined flow restoration (FR) and thrombectomy devices. Their use combines the advantages of intracranial stent deployment with immediate FR and a thrombectomy, which removes clot from the occluded artery. During deployment, the stent retriever compresses the thrombus and partially restores blood flow to the distal territory immediately. The entire device along with the thrombus is then removed. These devices have shown far superior results in large vessel occlusions compared

with other retrieval devices in terms of recanalization rates, clinical outcomes and low rates of symptomatic hemorrhage.[13] The Solitaire with intention for thrombectomy (SWIFT) study compared the efficacy of Solitaire FR stent retriever with the Merci device in AIS patients within 8 hours of symptom onset. The trial was halted a year sooner than planned because of significantly better outcomes in the Solitaire group (recanalization rates of 83.3% vs 48.1%, good clinical outcome in 58.2% vs 33.3%). Symptomatic hemorrhage and mortality were also significantly lower in the Solitaire group.[14]

Antiplatelet and Anticoagulant Drugs in Acute Ischemic Stroke

Aspirin should be given as soon as possible after an AIS. It reduces death or dependence when given within 48 hours of onset. If clopidogrel is used, a bolus dose of 300 mg (4 tablets of 75 mg each) is given for rapid inhibition of platelet aggregation. A daily dose of 75 mg takes up to 5 days for maximal platelet inhibition. Unfractionated and low molecular weight heparin (LMWH) is commonly used by physicians in AIS. However, their efficacy in AIS has not been established. In the large International Stroke Trial, subcutaneous heparin in AIS did not show any overall benefit over placebo in stroke outcome.[15] The only clear indication for anticoagulant therapy in AIS was for deep vein thrombosis (DVT) prophylaxis. These anticoagulants may, however, benefit the subset of patients with acute cardio-embolic stroke in whom the risk of early stroke recurrence is high. They are instituted prior to oral anticoagulant therapy. The latter is also recommended in AIS due to arterial dissection, cerebral venous sinus thrombosis and a hypercoagulable state.

GENERAL PRINCIPLES OF ACUTE STROKE MANAGEMENT

The focus on reperfusion therapy in recent times should not, in any way, detract from the importance of optimum medical management of AIS. To an obtunded patient with a severe stroke, intensive medical and nursing care is as vital, if not more, as reperfusion therapy.

Airway, Breathing and Circulation

The first step in managing an acute stroke patient is assessment of the vital signs. Arterial oxygenation (PaO_2) must be adequately maintained. It is prudent to administer oxygen through nasal prongs. Mechanical ventilation may be required if the patient is unable to protect his airway or has signs of raised ICP and impending herniation. Rapid sequence intubation is generally followed. It entails preoxygenation, Sellick maneuver (pressure applied to the larynx to compress the esophagus and prevent gastrointestinal reflux into lungs), and premedication with muscle relaxants to blunt the sympathetic response which causes a spurt in ICP. Noninvasive positive-pressure ventilator support is sometimes used instead of mechanical ventilation. Volume depletion must be quickly corrected. A central line is inserted to monitor CVP and IV fluids and pressor agents given as required. Normal saline infusion at 1–2 mL/kg per hour helps to maintain fluid balance.

Blood Pressure

Acute stroke patients usually have elevated BP. This is usually a compensatory mechanism to maintain normal cerebral blood flow in the presence of ischemia. Aggressive lowering of BP is detrimental in AIS as it compromises the cerebral perfusion pressure and increases the likelihood of converting the ischemic penumbra to an infarct. Antihypertensive medication is usually withheld unless BP is higher than 220/120 mm Hg. If thrombolytic therapy is contemplated, the BP should be less than 185/110 mm Hg. A parenteral beta-blocker like labatolol (bolus of 10–20 mg, repeated if necessary) or the calcium channel blocker nicardipine is used if the BP exceeds the above limits. A very high diastolic BP higher than 140 mm Hg may require sodium nitroprusside infusion to achieve a 10–20% reduction in diastolic BP. The practice of giving sublingual nifedipine should be strongly discouraged as it can cause a precipitous fall of BP with resultant cerebral ischemia. A rapid reduction of BP in AIS is only indicated if there is evidence of hypertensive encephalopathy, acute myocardial infarct/LV failure or acute renal damage. Arterial hypotension does not normally occur in AIS. If BP falls, it is important to exclude gastrointestinal bleeding, myocardial infarction, aortic dissection and volume depletion.

Blood Sugar and Temperature

Both hyperglycemia and hypoglycemia aggravate injury to already damaged neural tissue. Hyperglycemia results in a higher regional lactic acid production and decreased survival of penumbral tissue. In acute stroke, blood sugar level is maintained with subcutaneous boluses of plain insulin as per glucometer readings. Dextrose containing fluids are avoided. Sometimes, hypoglycemia mimics a stroke with an acute focal neurological deficit. Fever increases neural tissue metabolism and adversely affects outcome. Aspiration pneumonia and infection caused by urinary catheter and central line placement commonly occur in stroke patients. The temperature must be quickly lowered with antipyretics and antibiotics. Those with a high risk of aspiration should be fed through a nasogastric tube. Patients with persistent dysphagia will require a percutaneous feeding gastrostomy tube.

Deep Vein Thrombosis

A patient with dense hemiplegia has a high risk of developing DVT and pulmonary embolism. Precautions to prevent DVT include tight elastic stockings, intermittent calf pressure compression device and subcutaneous unfractionated

heparin (UFH)/low MW heparin. Every effort must also be made to mobilize the patient as early as possible.

MANAGEMENT OF STROKE COMPLICATIONS

Cerebral Edema

Cerebral edema is a leading cause of death in AIS, especially in the first week. It develops during the first 24–48 hours, peaks around 3–5 days after stroke onset and results in neurological deterioration. Large hemispheric infarcts are usually associated with significant cerebral edema. A big cerebellar infarct causes rapid brainstem compression, hydrocephalus and herniation, because the posterior fossa provides very little space to accommodate the edema. Judicious use of osmotic dehydrating agents like mannitol or hypertonic saline and mechanical hyperventilation help to reduce cerebral edema. The role of steroids in strokes is debatable. Although their efficacy has not been established, parenteral dexamethasone is often used by physicians concomitantly with mannitol to treat cerebral edema.

Malignant infarcts are large infarcts involving practically the entire ICA or MCA territory. They are associated with a high risk of brain herniation and death (80% mortality) with conventional treatment. Early decompressive hemicraniectomy (<48 hours of stroke onset) with removal of a large bone flap can be lifesaving in these cases.[16] Decompressive suboccipital craniectomy can, likewise, be lifesaving in a large cerebellar infarct.

Hemorrhagic Transformation of Infarct

Hemorrhagic transformation of an infarct occurs in 30–40% of AIS. The advent of thrombolytic therapy has increased the incidence of symptomatic hemorrhagic transformation. Heparin also increases this risk. If the hemorrhage is large and accompanied by clinical deterioration, the antiplatelet/antithrombotic medications must be discontinued and measures to reduce cerebral edema instituted. If a minor hemorrhagic transformation is seen on CT or MRI with no clinical deterioration, no specific intervention is required.

Seizures

Early seizures within 1–2 weeks of an AIS occur more often with large cortical infarcts, multiple infarcts, embolic stroke and venous infarcts. Associated metabolic disturbances also increase seizure risk. They can be the presenting feature of cerebral venous sinus thrombosis. An early seizure requires only a short-term antiepileptic drug treatment for about 3–6 months. Late onset seizures occurring 2 weeks after stroke onset are caused by gliosis and have a high recurrence rate with subsequent development of epilepsy. Hence, they require long-term therapy. Prophylactic anticonvulsant treatment in stroke patients is not recommended.

EMERGING THERAPIES IN ACUTE ISCHEMIC STROKE

Ultrasound Enhanced Thrombolysis

Experimental evidence suggests that ultrasound enhances the thrombolytic effect of IV rtPA. It causes disruption of a thrombus with greater penetration of thrombolytic material into the clot. Low frequency ultrasound exposure along with administration of microbubbles promoted clot lysis in AIS.[17] Continuous transcranial Doppler in IVT-treated patients was associated with a higher frequency of complete recanalization and clinical recovery compared to controls.

Neuroprotective Therapy

Several neuroprotective agents have undergone trials in AIS. However, to date, no agent has been found to improve outcome. Hypothermia has the potential of protecting the brain against anoxic-ischemic insults by reducing the metabolic need of underperfused brain tissue. Trials are ongoing, but various potential clinical barriers have arisen and hypothermia is not yet ready to be included in standard management protocols for AIS.

CEREBRAL VENOUS THROMBOSIS

Occlusion of a cerebral venous sinus or cortical vein by a thrombus can also result in stroke. Cerebral venous thrombosis (CVT) accounts for 0.5–1% of all strokes.[18] It occurs more commonly at a younger age and in women of child-bearing age because of pregnancy, puerperium and use of oral contraceptives (OC).

Etiology and Risk Factors

The etiological and predisposing factors can be broadly classified into genetic prothrombotic states and acquired conditions. Hereditary conditions with a high propensity for CVT include protein C, protein S and antithrombin III deficiency and homozygous mutations of factor V Leiden and prothrombin genes. Acquired predisposing situations include pregnancy, postpartum state, oral contraceptive pills (OCP), hyperhomocysteinemia and the antiphospholipid antibody (APLA) syndrome. Most pregnancy-related cases of CVT occur during the third trimester and the first 4 postpartum weeks. Use of OC pills is associated with a fourfold increased risk of CVT. This risk is even greater among those who also have a hereditary prothrombotic state. Hyperhomocysteinemia is another important cause of CVT, occurring more frequently in the Asian population.[19] With effective antibiotic therapy, the incidence of infection-related CVT has fallen dramatically. It now accounts for only 8% of cases.[20] However, infection from parameningeal sites (ear, sinus, mouth, face and neck) still plays an important role in children. The cavernous and lateral sinuses are the ones most frequently involved in the infective process. Other important predisposing conditions for CVT

include systemic lupus erythematosis, anemia, dehydration and malignancy. CVT is typically multifactorial with nearly 50% of patients possessing more than one risk factor.[21] The cause of CVT remains undetected in 20–30% of cases.

Clinical Presentation

Patients usually present with clinical features of raised ICP and focal neurological deficits. Headache is the most frequent symptom occurring in more than 80% of patients. Papilledema accompanies headache in about 50% of patients. Seizures, focal or generalized, occur in about 40% and are the presenting feature in 12–15% of CVT cases. About half of the patients are admitted to hospitals with impaired sensorium and altered mental state. Focal neurological deficits occur due to the presence of venous infarct or ICH. The clinical features depend on the location of the affected sinus. A superior sagittal sinus (SSS) thrombosis, besides causing headache and papilledema, produces a motor weakness predominantly of the lower limbs. Lateral sinus thrombosis results in a temporal lobe infarct with contralateral hemiparesis, aphasia and hemianopia. It is usually accompanied by fever, ear discharge and mastoid pain. Thrombosis of the deep cerebral venous system (the straight sinus, internal cerebral vein and vein of Galen) causes bilateral thalamic and basal ganglia infarcts. These patients present with rapidly deteriorating sensorium without focal deficit. Cavernous sinus thrombosis presents with orbital pain, proptosis, chemosis and affection of the III, IV and V cranial nerves. ICH occurs in 30–40% of CVT patients, even prior to anticoagulant use.[22] It is important to identify these patients to enable them to receive appropriate, timely treatment. Clues to a CVT etiology in these patients include presence of prodromal headaches (unusual for other ICH causes) and bilateral parenchymal involvement.

Cerebral venous thrombosis does not always cause a stroke. Patients may present more insidiously with clinical features of raised ICP without a focal deficit. They complain of headache, vomiting, papilledema and transient visual obscurations. This pattern closely resembles benign intracranial hypertension (BIH). In fact, CVT was detected in 10% of patients diagnosed as BIH.[23]

Diagnostic Approach

Cerebral venous thrombosis should be considered in all young stroke patients with no risk factors for ischemic stroke or with an unusual ICH. The presence of bilateral signs, seizures, headache and papilledema should raise the suspicion of DVT as they occur more frequently in venous infarcts compared to their arterial counterparts. In suspected CVT, laboratory investigations must include hemogram, biochemistry profile, PTT, aPTT, antiphospholipid antibodies and homocysteine. Infection must also be ruled out and, if in doubt, a CSF examination is ordered. A genetic thrombophilia screen includes estimation of protein C, protein S and antithrombin III, along with work-up for mutations of factor V Leiden and prothrombin gene.

Neuroimaging provides valuable information in CVT patients. A hyperdense signal on noncontrast CT scan suggests the presence of a thrombus in the venous sinus or cortical vein. "The empty delta sign" observed in a contrast enhanced CT scan consists of a central hypodensity or filling defect due to the thrombus, which is surrounded by contrast enhancement of the overlying walls of the sinus. It is triangular in shape and is visualized over the posterior aspect of SSS. An acute thrombus is difficult to detect on MRI in the first few days. However, by the second week it is easily visualized as an area of hyperintensity on T1- and T2-weighted sequences. Hemorrhagic infarcts and multifocal bleeds are easily detected on CT or MRI. A venous infarct is suspected if it is hemorrhagic, does not correspond to a well-defined arterial territory and reveals disproportionate mass effect and edema. The location of the infarct gives a clue to the thrombosed sinus. An infarct located in the frontal parasagittal cortex suggests an SSS thrombosis, while a temporal cortex infarct occurs with lateral sinus occlusion. Contrast enhanced MR-venography (MRV) is a rapid and reliable noninvasive method for diagnosing CVT. It accurately demonstrates absence of flow in the affected sinus. A digital subtraction angiography is usually not required when MRV is available. It is reserved for situations in which MRV is inconclusive or if an endovascular procedure is considered.

Management Options

The mainstay of treatment in acute CVT is systemic anticoagulation with UFH or LMWH, followed by oral anticoagulation. An IV infusion of UFH is titrated to keep aPTT at twice the control, while LMWH is given subcutaneously twice a day in a dose of 180 antifactor Xa units/kg per 24 hours. Generally, LMWH is preferred because of its ease of administration. Anticoagulants are given even in the presence of a hemorrhagic infarct or multifocal bleeds. A meta-analysis of UFH and LMWH trials confirmed the safety of anticoagulation with no occurrence of new or increased bleeding.[24] Long-term anticoagulation is usually with oral warfarin with adjustment of its dose to maintain INR between 2 and 3. Newer direct thrombin inhibitors like ximelogatran and argatroban are alternatives to warfarin. Oral anticoagulants are usually given for 3 months if CVT is due to a transient, reversible risk factor and 6–12 months if the cause is not known. Recurrent attacks of CVT and severe thrombophilias like antithrombin III deficiency or APLA syndrome may require indefinite, perhaps life long, therapy.

Endovascular local instillation of thrombolytic drug (urokinase or rtPA) directly into the affected sinus with or without mechanical removal of thrombus is considered in experienced centers for severe cases or those not improving with systemic anticoagulation. In fulminant cases with impending brain herniation, a decompressive hemicraniectomy could prove lifesaving.

Appropriate empirical antibiotic therapy along with surgical drainage of the infected source is instituted in

infection-induced CVT.[25] Women with CVT during pregnancy must receive LMWH in full dose throughout pregnancy and for at least 6 weeks postpartum. Only LMWH can be given as oral anticoagulants cause fetal embryopathy and are contraindicated in pregnancy. Though the course of CVT is unpredictable, a favorable outcome occurs in the majority of patients with complete recovery in about 80%.

INTRACEREBRAL HEMORRHAGE

Causes of Spontaneous Intracerebral Hemorrhage

Spontaneous ICH refers to bleeding in the brain parenchyma which is not caused by trauma. Hypertension is the commonest cause of ICH. It damages the walls of small penetrating arteries and arterioles 50–200 μ in diameter, especially at branch points. Hypertensive ICH has a predilection for certain anatomical sites corresponding to the location of these penetrating vessels. Putamen is the commonest site, followed by thalamus, superficial subcortical white matter (lobar), cerebellum and pons. Sometimes, underlying hypertension may be detected for the first time when ICH occurs. Rupture of arteriovenous malformations (AVMs) and aneurysms is suspected when ICH occurs at atypical sites in young people with no history of hypertension. Patients who are on anticoagulant and antiplatelet drugs also have an increased risk of ICH (0.5–2% risk of ICH with warfarin).[26] This risk increases in hypertensive, elderly patients. Thrombolytic therapy is also associated with high rates of hemorrhage (6.4% in the NINDS trial). Anticoagulant and thrombolysis induced bleeds are large, multifocal (cortical and subcortical) and often contain a blood fluid level. Amyloid angiopathy is a common cause of ICH in elderly patients over 65 years. Deposition of β-amyloid protein in small arteries and arterioles of leptomeningeal vessels makes them fragile and prone to bleed. Amyloid bleeds are usually lobar (superficial cortical), occur at multiple sites and are often recurrent. Other causes of ICH include bleeding diathesis (thrombocytopenia), bleed in a tumor, vasculitis and use of cocaine and other sympathomimetic drugs.

Important Sequelae of Intracerebral Hemorrhage

Increase in Hematoma Size

A significant increase in size of the hematoma occurs within the first few hours of onset in about one-third of patients, more so in the first 6 hours. This causes a fairly rapid neurological deterioration in these first few hours. It is not clear whether hypertension contributes to this increase. Antiplatelets and anticoagulants increase the risk of significant ICH expansion. Extravasation of contrast within the hematoma on CTA or MRI is called the spot sign. It represents ongoing hemorrhage and is a strong predictor of hematoma expansion.[27]

Perihematoma Cerebral Edema

Cerebral edema usually manifests after 24–48 hours and is maximal by the 3rd–5th day or even later in some cases. It is an inevitable sequel of the interaction of blood and blood products within brain tissue. Besides direct mechanical injury to brain tissue by the expanding clot, decreased blood flow in the immediate surrounding area of the hematoma also occurs. This releases inflammatory cytokines and excitatory amino acids with resultant breakdown of the blood-brain barrier and increase in cerebral edema.

Hydrocephalus

Intraventricular hemorrhage (IVH) occurs in approximately one-third of cases of ICH, mainly due to seepage of blood into the ventricles. In few cases, it may occur as a primary event. IVH can obstruct CSF pathways and cause hydrocephalus. Thalamic and cerebellar hematomas are also likely to cause hydrocephalus by obstructing the III and IV ventricles respectively.

Diagnosis of Intracerebral Hemorrhage

Intracerebral hemorrhage presents abruptly with severe headache, vomiting and a rapidly deteriorating sensorium. A history of hypertension, recent discontinuation of antihypertensive drugs, head trauma, use of antiplatelets or anticoagulants and drug/alcohol abuse must be elicited from the patient or caregiver. Focal neurological deficits depend on the location of the hematoma. A putaminal bleed presents with contralateral hemiparesis with conjugate eye deviation toward the ipsilateral hemisphere. Patients with pontine hemorrhage are usually stuporous or comatose with quadriparesis, pinpoint pupils and hyperpyrexia. Cerebellar hemorrhage presents acutely with repeated vomiting, vertigo and ataxia.

CT scan of the head is the preferred imaging modality in ICH. It is quick, easily available and adequately detects the presence, location and size of the hematoma. Cerebral edema, hydrocephalus and mass effect are also well-visualized. Serial CT scans are performed to look for hematoma expansion or increasing cerebral edema. Gradient echo sequence on MRI scan detects punctate microhemorrhages which are not seen on CT scan. A lobar location of these microhemorrhages points to a cerebral amyloid angiopathy while deep ones occur in chronic hypertension. If the hematoma is in an unusual location or has odd features, a contrast-enhanced CTA/MRA is performed to look for an underlying aneurysm, AVM or neoplasm. A hematoma due to aneurysmal rupture is located either in the frontal or temporal lobe, largely within and around the Sylvian fissure. A DSA is the gold standard for identifying aneurysms and AVMs and may be required in some cases (Figs 6 to 8).

MANAGEMENT OF INTRACEREBRAL HEMORRHAGE

Intracerebral hemorrhage patients are often admitted in a stuporous or comatose state with unstable vital signs. Emergent measures to maintain hemodynamic stability must

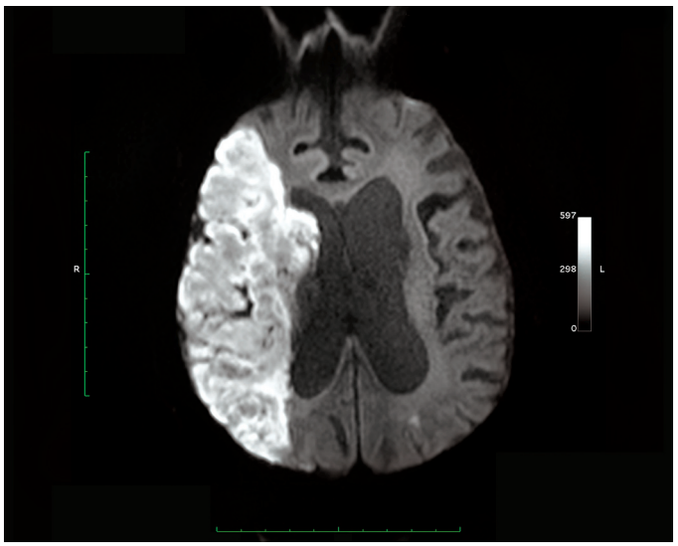

Fig. 6: Cerebral infarct: MRI diffusion weighted images reveal a large area of diffusion restriction in the right MCA and watershed territories representing an acute infarct

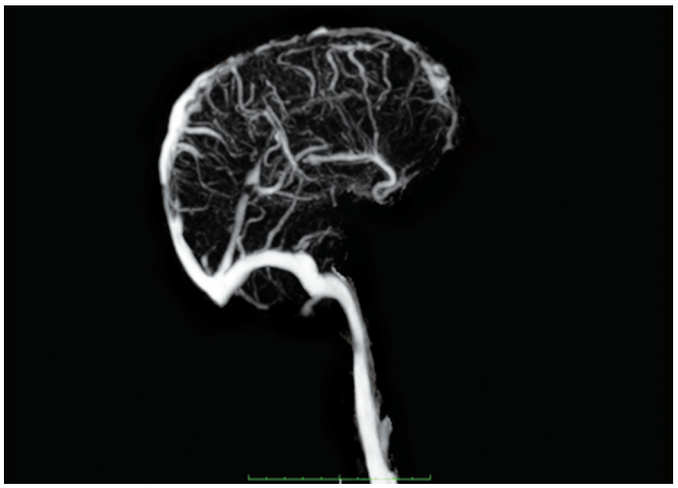

Fig. 7: Venous infarct: MR venogram reveals a large thrombus in the superior sagittal sinus

take precedence over all other therapeutic considerations. For more details, please refer to the earlier Section on General Principles of Acute Stroke Management.

Blood Pressure Management

Hypertension almost invariably occurs after ICH. This acute hypertensive response typically declines by about 2 mm Hg mean arterial pressure (MAP) per hour within 6 hours of acute bleed, reaching a plateau by 24 hours.[28] A persistently high BP carries the theoretical risk of increasing hematoma size. A rapid 15–20% reduction in BP in small to moderate sized hematomas was shown to be safe and beneficial. The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) study also showed that early intensive BP lowering treatment was well-tolerated and resulted in reduced

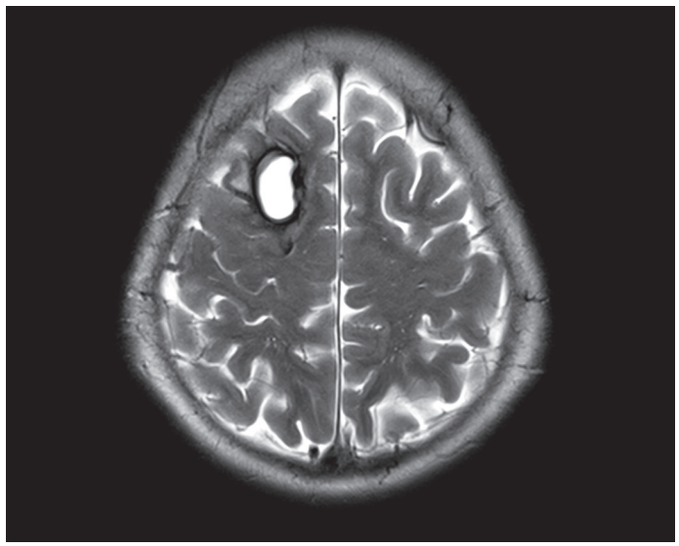

Fig. 8: Venous infarct: MRI reveals right frontoparietal hemorrhage

hematoma growth.[29] However, overaggressive BP-lowering in patients with raised ICP may reduce CPP and worsen brain injury. An acute lowering of BP is considered when the MAP is higher than 130 mm Hg or systolic BP is higher than 180 mm Hg. The aim is to lower levels to around 160/90 mm Hg or MAP of 110 mm Hg. If ICP is concomitantly elevated, then BP is lowered by first reducing ICP.

If the systolic BP is higher than or equal to 200 mm Hg or MAP is higher than or equal to 150 mm Hg, then aggressive BP reduction is warranted with continuous IV infusion of antihypertensives and BP monitoring every 5 minutes. Because BP tends to decline naturally after ICH, short-acting agents are used. Labetalol is the preferred drug. Alternatives to labetalol include enalaprilat, nicardipine and esmolol. Sodium nitropruside is usually avoided as it tends to increase ICP by vasodilatation. It is, however, used as an emergency medication when BP is higher than 240/140 mm Hg or when other agents fail to lower it.

Raised ICP and Seizures

Raised ICP in acute ICH is due to expanding hematoma size in the first few hours and cerebral edema after 24 hours of onset. Hydrocephalus also increases ICP. The therapy for raised ICP has been dealt with in the subchapter Raised Intracrenial Pressure of Chapter Neurological Problems. Early seizures occur in patients with a lobar hematoma. Deep-seated hemorrhage is usually not associated with seizures. Prophylactic use of anticonvulsants is not indicated for ICH patients, except in lobar hematomas where their use is considered optional.

Factor VIIa in Acute ICH

Recombinant factor VIIa (rFVIIa) acts on factor X on the surface of platelets, activating it and facilitating clot formation. It is

meant to stop hematoma growth. Clinical trials of this drug in acute ICH showed that though factor VIIa exerted biological effects and reduced hematoma size, it did not significantly improve patient survival or functional outcome. In fact, the incidence of thromboembolic events increased with this drug.[30] Based on these results, the routine use of rFVIIa for all patients with ICH within a 4-hour time window cannot be recommended. However, rFVIIa may still be useful in a subset of patients who present within $2^1/_2$ hours of ICH onset, have relatively small bleed (<60 mL) and are less than 70 years.[31]

Reversal of Anticoagulant and Thrombolytic Induced ICH

Warfarin-induced ICH requires discontinuation of the drug and immediate administration of IV vitamin K (10 mg slowly over 30 minutes). It, however, has a delayed onset of action of 6–24 hours. Prothrombin complex concentrate (PCC) comprising factors II, IX, X, with or without factor VII, should be given if available. It corrects INR rapidly within 10 minutes of its administration. If PCC is not available, fresh frozen plasma (FFP) is used in a dose of 15 mL/kg. It has a slower onset of action than PCC and requires infusion of a large volume which can cause volume overload. Cross-matching and thawing of the solution also use up valuable time. Factor VIIa has also shown benefit in anticoagulant-induced ICH. It is reported to reverse very high INRs and/or bleeding in patients on warfarin as early as 15 minutes after an IV bolus.

In ICH due to heparin or low MW heparin, IV protamine sulfate is given in a dose of 1 mg/100 units of heparin. The anticoagulant effect of heparin is reversed within 5 minutes of administration. This drug is given by a slow injection at a rate of less than 50 mg every 10 minutes to prevent hypotension. In patients with a high risk of embolic stroke like a prosthetic heart valve, oral anticoagulants can be restarted after 10–15 days of the bleed. ICH caused by antiplatelet drugs (especially dual antiplatelet therapy) can be treated by platelet transfusions and desmopressin which reportedly improves platelet activity and increases plasma factor VIII levels. Thrombolysis-induced ICH is treated by immediately stopping the rtPA infusion, followed by 6–8 units of platelet transfusions or FFP and 6–8 units of cryoprecipitate containing factor VIII. No therapy has, however, proved beneficial and the outcome is very poor.

15

SURGERY IN INTRACEREBRAL HEMORRHAGE

A cerebellar hematoma larger than 3 cm in size, with clinical deterioration, brainstem compression or hydrocephalus, must be urgently evacuated. This is because the cerebellum lies in a tight compartment and there is a high risk of transtentorial herniation if it is not removed. Patients with lobar hematomas greater than 30 mL, within 1 cm of the surface, and who are clinically deteriorating, should also be given the option of surgical evacuation. Being close to the surface, it is relatively easy and safe to evacuate them and the results are generally favorable. The site of the lobar hematoma also influences management decisions. A large hemorrhage may be comfortably accommodated in the occipital lobe. A similar-sized hematoma in the temporal lobe could produce a midline shift and require surgical evacuation.

The benefit of surgically evacuating other supratentorial hematomas has not been established. The multicenter surgical treatment for intracerebral hemorrhage (STICH) trial did not report a clear benefit of surgery in supratentorial ICH with the exception of lobar hematomas.[32] However, most patients in this trial underwent evacuation 12 hours and sometimes even 36 hours after ICH. Early evacuation of hematoma could result in better clinical outcomes as it would reduce perihematoma ischemia and toxic effects of blood products, thereby preventing or minimizing cerebral edema. Decompressive hemicraniectomy is indicated in large supratentorial bleeds with significant mass effect, midline shift and imminent danger of herniation. Removal of a wide bone flap can be lifesaving in such situations. Evacuation of clot can be simultaneously attempted.

Newer minimally invasive surgical procedures to evacuate deepseated hematomas are being increasingly performed. They minimize trauma to the nearby brain tissue and reduce operative time. Stereotactic aspiration of the clot entails placing a catheter stereotactically into the core of the hematoma. Urokinase or tPA is then injected locally. This liquefies the clot which is then aspirated out. Significant reduction in hematoma size and improved clinical outcomes has been reported with this technique.[33] The neuroendoscope is also a promising tool for hematoma evacuation. It is introduced through a small burr-hole and has the added ability to coagulate the bleeding vessel.[34]

In IVH, an external ventricular drain (EVD), is placed to drain out the blood. Intraventricular infusion of urokinase is used to hasten clot lysis. A recent randomized trial reported a significantly higher clot resolution rate with intraventricular instillation of rtPA through an EVD, compared to placebo in patients with large IVH. There was also a trend toward a favorable outcome in the treated group.[35] Hydrocephalus secondary to thalamic or cerebellar hematomas or IVH may initially require an EVD, with subsequent shunt surgery if required.

SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage accounts for 5–10% of all strokes. While head injury is the commonest cause, rupture of intracranial saccular aneurysms (aneurysmal SAH) is the most frequent nontraumatic cause. Acute SAH carries a high mortality of 50% at 30 days,[36] with nearly 10% succumbing before they can receive any medical attention. The discussion in this section relates only to aneurysmal SAH.

Clinical Presentation

Acute SAH typically presents with a sudden onset of explosive "thunderclap" headache which is maximal at onset.

Patients describe it as the "worst headache of their lives". It is accompanied by profuse vomiting, neck stiffness and altered sensorium ranging from confusion to coma. A transient loss of consciousness sometimes occurs at the onset due to an acute spike in ICP. Fever can be caused by the presence of blood in the subarachnoid space. A subhyaloid retinal hemorrhage may be seen on fundus examination. Focal neurologic deficits like hemiparesis and aphasia indicate the presence of an associated intraparenchymal hematoma. Unruptured aneurysms may sometimes be detected on neurological testing. An ipsilateral third nerve paresis with a dilated, nonreactive pupil suggests a posterior communicating artery aneurysm. Bitemporal field defect due to optic chiasmal compression occurs with a supraclinoid carotid aneurysm, while occipital or neck pain may indicate a posterior circulation aneurysm.

The Hunt and Hess classification is a useful guide to prognosis and management options in SAH.

Hunt and Hess Clinical Classification of SAH

- Asymptomatic or mild headache with slight neck stiffness.
- Severe headache, stiff neck, no focal deficit except for cranial nerve palsies.
- Drowsy or confused, mild neurologic deficit.
- Stuporous, moderate to severe hemiparesis.
- Coma, decerebrate posturing.

Diagnosis

All patients with sudden severe unexplained headache must be evaluated for possible SAH. A noncontrast CT scan of head is the investigation of choice in suspected cases. It identifies nearly all cases in the first 24–48 hours. Its sensitivity in detecting SAH decreases as time elapses. At the end of 1 week, SAH can be detected in only about 50% of cases. Subarachnoid blood is usually seen in the basal cisterns, Sylvian fissures, interhemispheric fissure and perimesencephalic cisterns. If it occurs more over the hemispheres than the basal cisterns, an AVM or mycotic aneurysm should be suspected. Associated parenchymal hematoma and hydrocephalus may also be seen.

If the clinical history suggests SAH and CT scan fails to detect blood, a lumbar puncture (LP) must be done. CSF examination reveals innumerable red blood cells (RBCs). Xanthochromia is seen on a spin CSF specimen and helps to differentiate a subarachnoid bleed from a traumatic spinal tap. Xanthochromia may not be seen if LP is done within 6 hours of the hemorrhage.

Once SAH is diagnosed, a four-vessel DSA is performed to confirm the presence, size, location and other morphologic characteristics of the aneurysm. It can also detect a focal cerebral vasospasm. CTA and MRA are alternative noninvasive means to detect an aneurysm. If an initial angiogram fails to show an aneurysm, it may be repeated after 2–3 weeks. In about 10% of cases, subarachnoid blood is restricted to the perimesencephalic cistern (cistern around the midbrain). Blood is not seen in the Sylvian fissures or other locations. About two-thirds of these bleeds have normal angiograms with no detectable aneurysm. They are unlikely to rebleed and carry a significantly better prognosis than other forms of SAH.

MANAGEMENT OF ACUTE SAH

Initial Management

The patient should be admitted to ICU for close monitoring and kept in a quiet room. Headache must be treated with appropriate analgesics. Sometimes, mild analgesics like paracetamol may suffice. Salicylates are better avoided because of their inhibitory effect on hemostasis. If the pain is severe, codeine or a synthetic opiate like tramadol may be given. In smokers, chest physiotherapy and nebulization help to minimize coughing. Stool softeners are given to avoid straining at stools. These precautions aim to minimize the risk of rebleed.

Blood pressure should be carefully monitored and lowered to less than 140 mm Hg systolic using IV labetalol or nicardipine. If signs of raised ICP are present, measures to lower it must be first instituted before trying to lower BP. Volume depletion brought on by profuse vomiting and obtunded state must be corrected. Serum electrolytes are regularly monitored as hyponatremia commonly occurs in SAH. A baseline ECG sometimes shows changes simulating acute myocardial ischemia. A normal creatine kinase myocardial band (CK-MB) fraction excludes myocardial damage in this setting.

Oral nimodipine 60 mg every 4 hours for 21 days is given prophylactically to reduce the risk of delayed vasospasm and ischemic stroke. Prophylactic anticonvulsants (phenytoin or levetiracetam) are started as the occurrence of a seizure increases the risk of a rebleed. They should be given only for a short period and discontinued after the aneurysm is clipped or coiled. Patients in Grades IV and V have a high surgical mortality risk and need to be managed conservatively till their sensorium improves.

Treating the Aneurysm

The definitive treatment of aneurysmal SAH consists of either microsurgical clipping or endovascular coiling of the aneurysm. Surgery is the more definitive treatment. The operating microscope has made surgery safe and effective. It is especially useful when the aneurysm is located at the trifurcation of the MCA, has a size of more than 1 cm or a wide neck. Early surgery within 3 days of the initial bleed and, if possible, within 24 hours is recommended in conscious and hemodynamically stable patients. Early surgery, by removing the clot around the artery, also minimizes the threat of delayed vasospasm. Coiling with platinum (Guglielmi detachable) coils is preferred for posterior circulation aneurysms, small narrow necked anterior circulation aneurysms and those situated in other technically difficult locations. It is particularly useful in elderly patients with significant medical comorbidities where surgery is contraindicated.

COMPLICATIONS OF SAH

Rebleeding

Urgency in the treatment of SAH arises because of the high incidence of potentially fatal rebleeding in the first few days after SAH. About 25% of SAH patients have a rebleed in the first 24 hours. Mortality as high as 80% has been reported with rebleeding.[37] So, it is imperative that SAH patients (Grade III or less) undergo angiography and definitive treatment (surgery or clipping) as early as possible. Delaying treatment also makes them more vulnerable to vasospasm. The use of antifibrinolytics like epsilon aminocaproic acid (EACA) to prevent rebleed has largely been given up because of the lack of efficacy and high incidence of cerebral ischemia. However, in some cases, early treatment with a short course of EACA till surgery or coiling is completed, has been advocated.[38]

Delayed Vasospasm

Delayed ischemic neurologic deficits are caused by the presence of blood in the cisterns with resultant constriction of blood vessels. About 20–40% of patients with SAH develop clinically significant vasospasm. Its incidence peaks between the 7th and 14th day of SAH, but can occur up to 21 days postbleed. The risk of vasospasm is directly proportional to the amount of subarachnoid blood seen on the initial CT scan.[39] A thick layer of blood in the fissures more than 1 mm thick and clots larger than 5 x 3 mm in the basal cisterns significantly increase the risk of subsequent vasospasm. The clinical manifestations depend on the vessels involved and the extent of vasospasm. They range from minor neurological deficits to large, disabling strokes.

Preventing vasospasm is a priority. Early institution of oral nimodipine reduces the risk of vasospasm. Dehydration and volume depletion must be avoided with judicious use of IV fluids. However, prophylactic hypervolemia is not indicated. Hypomagnesemia occurs in more than 50% of SAH patients and increases the risk of delayed cerebral ischemia.[40] Transcranial Doppler is a useful tool to monitor cerebral blood flow velocities in intracranial vessels. Increasing velocities on serial measurements indicate early vasospasm which may precede the onset of neurologic signs by 24–48 hours, thus allowing early therapy.

In an established vasospasm, the Triple-H therapy (hypervolemia, induced hypertension, hemodilution) has shown benefit. However, this treatment can be instituted only after surgery or clipping of the aneurysm. If done before definitive treatment, the risk of rebleeding is increased. After securing the aneurysm, BP can be increased to 160–180 mm Hg with judicious use of vasopressors like dopamine or norepinephrine and volume expanders. Colloids like albumin provide additional benefit by causing hemodilution. The aim of hemodilution is to keep hematocrit at 30–32% to reduce viscosity while maintaining oxygen carrying capacity. In a recent systematic review, hypertension was found more effective in increasing cerebral blood flow than hemodilution and hypervolemia.[41] In refractory cases of vasospasm, interventional therapy with intra-arterial balloon angioplasty and intra-arterial vasodilators is considered.[42] Intra-arterial agents currently used are calcium channel blockers, verapamil and nicardipine and papaverine. Balloon angioplasty of vasospastic vessels is also a viable option, but carries a significant risk of rupture or dissection of the vessel. It is used for spasm of proximal vessels, while super-selective intra-arterial vasodilator injections are used for distal spasms.

Hydrocephalus

The presence of dense blood in the basal cisterns or ventricles obstructs CSF pathways, causing hydrocephalus. It presents with a relatively abrupt onset or persistence of stupor or coma after the initial rupture. It requires ventricular drainage of CSF through an EVD. In most cases, it resolves after the acute phase, but if it persists, a ventriculoperitoneal shunt is placed.

Hyponatremia

Hyponatremia in SAH is caused in most cases by cerebral salt wasting, though SIADH can also occur. Serum and urine osmolality and urine spot sodium help to clarify the cause of hyponatremia. The treatment for SIADH is fluid restriction while cerebral salt wasting is treated by aggressive fluid replacement with normal saline or hypertonic 3% saline. Because SIADH and cerebral salt wasting often coexist, the rational way of treating hyponatremia would be adequate sodium and volume replacement with restriction of free water.

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D. Central Nervous System Infections

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INTRODUCTION

The era of antibiotics was ushered in nearly 70 years ago with the discovery of penicillin. Since then, giant strides have been made in the development of effective and relatively safe antimicrobial agents to treat neurological infections, in particular, bacterial meningitis. Yet, they remain an important worldwide cause of morbidity and mortality. Acute fulminant infections like meningitis, encephalitis, brain abscess and subdural empyema continue to claim several lives. The critical care of these infections requires the close collaboration of the intensivist, neurologist, microbiologist, neuroradiologist and a well-trained nursing staff. This section will focus on central nervous system (CNS) infections which present acutely and run a fulminant course.

GENERAL CONSIDERATIONS

Some important factors contributing to the threat posed by CNS infections in recent times are as follows: (1) the burgeoning number of immunocompromised patients worldwide due to the global epidemic of acquired immune deficiency syndrome (AIDS) and the increasing use of aggressive immunosuppressive therapy; (2) increasing numbers of antibiotic-resistant organisms due to widespread and often indiscriminate use of antimicrobials; (3) frequent international travel which has facilitated the global spread of emerging infections. On a positive note, the effective, widespread use of *Haemophilus influenzae* vaccine has resulted in a sharp decline in the worldwide incidence of community-acquired bacterial meningitis in children, limiting it largely to the infant, adult and elderly populations.

Early diagnosis and rational empirical therapy are the cornerstones of management in suspected CNS infection. Keeping the treatable conditions in mind, the physician must address the following issues: (1) appropriate antibiotics to combat the common community acquired pathogens *Streptococcus pneumoniae* and *Neisseria meningitidis;* (2) need to treat Gram-negative bacteria in certain situations; (3) treatment of *Listeria monocytogenes* in elderly and immunocompromised patients and (4) acyclovir for possible viral herpes simplex virus (HSV) encephalitis.

ACUTE MENINGITIS

Etiology and Risk Factors

Bacterial and viral meningitis are the two most frequent causes of acute meningitis. The term aseptic meningitis refers to meningeal involvement due to nonpyogenic bacterial infections and other causes like systemic lupus erythematosus (SLE), sarcoidosis and drugs. Acute bacterial meningitis (ABM) is commonly caused by hematogenous spread of bacteria from a distant site of infection. Other routes of entry include contiguous spread of infection from neighboring sites (sinusitis, otitis media, mastoiditis) and direct CNS inoculation following neurosurgery or a penetrating head injury. Congenital or acquired defects in the skull or spine cause recurrent attacks of meningitis.

In community-acquired ABM in children and adults, *S. pneumoniae* and *N. meningitidis* are the most common organisms, together accounting for 90% of cases. Other less common organisms include *L. monocytogenes,* group B streptococci and *H. influenzae.* Pneumococcal meningitis is responsible for more than half of all cases at all ages except for infants less than 2 months of age.[1] Over half of these patients have sinusitis or pneumonia at presentation. Immunoglobulin deficiency, sickle cell disease, splenectomy, alcoholism, diabetes and CSF leaks increase the risk of acquiring this infection.[2] Meningococcal meningitis caused by *N. meningitidis* is the most frequent cause of meningitis in children and young adults. It is highly contagious and small epidemics have occurred during overcrowding in dormitories, boarding schools and military bases and also among household contacts.[3] *L. monocytogenes* meningitis tends to occur in elderly people over the age of 55 years, third trimester pregnant women, infants less than 3 months of age and people with impaired T cell immunity (chronic corticosteroid therapy, HIV). Outbreaks of this meningitis are often food borne. These bacteria are known to contaminate soft cheese, unpasteurized milk, hot dogs and luncheon meat.

Though Gram-negative bacilli (*E. coli, Pseudomonas*, *Acinetobacter*, *Klebsiella*) cause only 3% of community-acquired meningitis, they are responsible for one-third of all nosocomial infections. *Staphylococcus aureus* is the other common pathogen in the nosocomial group.[4] If ABM is secondary to frontal or maxillary sinusitis and mastoiditis, anaerobic infection must also be kept in mind. Penetrating head injury and neurosurgical procedures like external ventricular drain (EVD) and shunt placement predispose to infection by *S. aureus,* Gram-negative bacilli, skin organisms (*S. epidermidis*) and anaerobes. Neutropenic patients are susceptible to *Pseudomonas* and *E. coli* infection.

Viral meningitis is by far the most common cause of acute meningitis. It occurs with a higher frequency than all other causes of meningitis put together.[5] Enteroviruses (mainly coxsackie and echovirus) account for the majority of cases, mainly during the late summer months. HSV-2 and varicella zoster virus (VZV) meningitis occur sporadically throughout the year, while mumps and lymphocytic choriomeningitis virus infections predominate in winter. HSV-2 causes genital herpes as well as recurrent attacks of meningitis. About 5–10% of patients with acute HIV infection develop aseptic meningitis during the early stage of illness, usually at the time of seroconversion.[6] Tuberculous meningitis (TBM) and fungal

meningitis usually cause a subacute or chronic infection. However, they sometimes present acutely and run a fulminant course. They must be considered in the differential diagnosis of acute meningitis.

Noninfectious causes of acute meningitis include collagen vascular disease (SLE and Sjogren's), sarcoidosis, Wegener's granulomatosis and polyarteritis nodosa. A toxic meningitis follows the use of intrathecal agents, intravenous immunoglobulin (IVIg), measles, mumps and rubella (MMR) vaccine, and muromonab CD3 (OKT3). Carcinomatous and lymphomatous meningitis must also be considered in the differential diagnosis of acute meningitis and cytology for malignant cells in the CSF must be asked for.

Clinical Presentation

Patients typically present with acute headache, fever, photophobia, vomiting and an altered level of consciousness. This is particularly so with ABM. Rapid clinical deterioration often occurs within hours or, at most, in a day or two. Nearly two-thirds of patients with ABM have an altered sensorium, with about 20% in coma. This differentiates ABM from viral meningitis which runs a relatively benign course with preserved consciousness, unless encephalitis coexists. Patients with viral meningitis can, however, present with severe headache and repeated vomiting which require hospitalization and parenteral analgesics. New onset seizures occur in about 20% of patients with bacterial meningitis and carry a worse prognosis. They occur more frequently in children, being the presenting feature in one-third of them.[7] The presence of seizures also raises the possibility of HSV-1 encephalitis and patients must be given the benefit of acyclovir till the definitive diagnosis is made.

Neck stiffness (resistance to passive flexion of the neck), together with Kernig's sign and Brudzinski's sign are the classic tests for meningeal irritation. If present, they strongly suggest meningitis. However, these tests have a low sensitivity. So absence of these signs does not in any way exclude the diagnosis of meningitis.[8] Elderly patients with a degenerative cervical spine also have a stiff neck, but the differentiating point is that, in them, resistance to neck movement occurs in all directions and not only on flexion as seen in meningitis. Focal neurologic deficits generally do not occur in acute meningitis. If they do, other conditions like brain abscess, encephalitis or cerebrovascular complications must be considered. However, *L. monocytogenes* meningitis can be associated with cranial nerve involvement, ataxia, nystagmus and other brainstem signs suggestive of a rhombencephalitis syndrome. A painful, predominantly unilateral ophthalmoplegia with chemosis, proptosis and visual impairment suggests cavernous sinus thrombosis. Infections of the paranasal sinuses, nasopharynx or facial soft tissues around the eye and nose are largely responsible for its occurrence.

Clues from the history and examination of the patient often provide an insight into the etiology of the meningitis. A history of close contact with another person with a similar illness raises the suspicion of meningococcal meningitis. Gastrointestinal disturbance, including diarrhea, often accompanies enteroviral meningitis. A history of CSF rhinorrhea or otorrhea following head injury points to a fracture of the skull base and increases the risk of meningitis. If a careful history is elicited, it is observed that most TBM patients have had a low grade persistent fever with headache for at least 3–4 weeks prior, which has been labeled as "viral" or "typhoid" and treated with a concoction of antibiotics. Precious time is thus lost. The thick fibrous exudates covering the base of the brain result in hydrocephalus and vasculitis, with blood vessel occlusion and stroke. Presence of a skin rash points to the diagnosis of meningococcal meningitis. A diffuse, erythematous, maculopapular eruption at onset evolves to a hemorrhagic purpuric rash over the trunk and lower limbs. Children with recurrent bouts of meningitis must be examined for anatomical defects like a meningocele or spina bifida. Meningitis can be deceptively asymptomatic in the very young, very old and immunocompromised patients in whom headache and fever may be absent. Confusion or altered sensorium may be the only sign of meningitis in these patients. Hence, a high index of suspicion is required and the threshold for lumbar puncture (LP) should be low for these patients.

Laboratory Diagnosis

Serum inflammatory markers like C-reactive protein (CRP) and procalcitonin are significantly elevated in bacterial meningitis compared to viral. Blood cultures must always be ordered prior to initiating empirical antibiotic therapy in suspected bacterial meningitis. They test positive in about 50% of cases caused by the three common bacteria. They reveal the causative organism even when CSF cultures are negative, underscoring their utility and importance in acute meningitis.

The definitive diagnosis of meningitis is made by analysis of CSF. The first CSF examination is invariably the most revealing one and must include opening pressure manometry, a glucose ratio (obtain a concurrent blood glucose sample), cell count, smears for relevant microbiology and immunostaining and appropriate CSF cultures. An LP is safely carried out if the patient is under 60 years of age, immunocompetent, able to correctly follow two consecutive commands and has had no recent seizure.[9] If any of the above criteria are not met, a CT or MRI scan is carried out prior to LP. In the absence of a mass lesion or obstructive hydrocephalus, a guarded LP can be done even with elevated intracranial pressure (ICP). There should be no delay between CSF collection and examination, because cells adhere to the collecting tube over time, causing falsely low cell counts.

Typically, the CSF in ABM is turbid with a raised opening pressure, increased white blood cells (WBC) count in thousands, mainly polymorphonuclear, elevated proteins (100–500 mg%) and a low CSF: blood glucose ratio less than 50%. Independent predictors of bacterial meningitis with more than 99% certainty include CSF: serum glucose ratio less than 0.23, glucose less than 34 mg%, proteins more than 220 mg%, WBC more than 2,000 cells and polymorphs more than

1180 cells.[10] In immunocompromised patients the CSF cell count, glucose and proteins may only be mildly abnormal.

The specific infecting organism can be identified by Gram stain, culture and polymerase chain reaction (PCR). Gram stain enables a rapid, initial detection of the organism, but requires a concentration of about 100,000 organisms/mm^3 to be positive. Bacterial culture identifies the organism in about 70% of cases along with its antibiotic sensitivity. Broad-based, multiprobe PCRs that detect bacterial deoxyribonucleic acid (DNA) within 3 hours for the three common bacterial pathogens and listeria are available. However, unlike cultures, they do not provide data on antibiotic sensitivity. The lab diagnosis of TBM is generally unsatisfactory. AFB is detected in very few CSF samples, PCR has a diagnostic reliability of only 50% and culture requires up to 7 weeks to grow the organism. Hence, therapy for TBM is usually started empirically. A chest X-ray may detect military tubercles or a cavitatory lesion. CT or MRI shows thick, basal exudates with associated tuberculomas and hydrocephalus.

The CSF in viral meningitis reveals normal sugar with mildly elevated proteins and a lymphocytic pleocytosis. Polymorphonuclear predominance may be seen in the first 24–48 hours of the infection. CSF PCR is sensitive and specific for the diagnosis of meningitis due to herpes virus, enterovirus and some arboviruses. Detection of IgM antibodies in CSF helps to identify VZV and West Nile virus (WNV) infections. Serological tests also aid in diagnosis. A positive serum IgM or a fourfold increase in IgG levels in paired serum samples (acute and convalescent sera) collected 4 weeks apart is diagnostic for HSV, VZV, Japanese encephalitis (JE) virus and Epstein-Barr virus (EBV). Although viral meningitis is usually self-limiting, its proper diagnosis is of clinical value as it limits other diagnostic testing.

Management of Acute Meningitis

A patient with suspected acute meningitis must be urgently admitted to the hospital, preferably in the ICU, if seizures, altered mental state or raised ICP are present. Bacterial meningitis has to be considered first, above all other conditions. The institution of antimicrobial therapy must be swift. Lost time can prove extremely costly in terms of neurologic sequelae. A rapid general and neurological examination on admission aims to identify the source of infection, any underlying illness and contraindication to LP. Blood is collected for routine biochemistry including hemogram, smear for malarial parasite (MP), erythrocyte sedimentation rate (ESR), liver and renal functions, coagulation profile, HIV, ANA, venereal disease research laboratory (VDRL), CRP and procalcitonin levels. A blood culture is urgently asked for. This is the only investigation that must precede antibiotic therapy. If there are no contraindications (mentioned earlier), an LP is performed just before commencing the therapy. If a CT or MRI is required prior to LP, empirical antibiotics are started first, followed by neuroimaging and LP.

Table 1: Empirical antibiotic therapy of acute bacterial meningitis

Age and associated conditions	*Likely organisms*	*antibiotics*
Children and adults	*S. pneumoniae* *N. meningitids*	Ceftriaxone or cefotaxime + vancomycin
Adults over 55 years	*S. pneumoniae* *L. monocytogenes* *H. influenzae*	Ceftriaxone or cefotaxime + vancomycin + ampicillin
Meningitis with sinusitis, otitis media or known CSF leak	*S. pneumoniae* Gram-negative bacilli *S. aureus* Anaerobes *H. influenzae*	Ceftazidime + vancomycin + metronidazole
Penetrating head trauma, neurological procedures	*S. aureus* *S. epidermis* Gram-negative bacilli	Vancomycin + ceftazidime or Vancomycin + meropenem
Immunocompromised state	*L. monocytogenes* Gram-negative bacilli *S. pneumoniae*	Ceftazidime + ampicillin + vancomycin
Nosocomial infection	Gram-negative bacilli *S. aureus*	Vancomycin + ceftazidime

Empirical Antibiotic Therapy

Empirical antibiotic therapy is the cornerstone of acute meningitis management. The choice of antimicrobials depends on the likely causative organism, which in turn depends on the age and immune status of the patient and whether the infection is nosocomial or community acquired (Table 1). It is presumed that *S. pneumoniae* is resistant to penicillin and *S. aureus* is methicillin resistant. So, treatment is initiated with vancomycin and a third generation cephalosporin. If sinusitis, otitis media or mastoiditis is the probable cause, adequate coverage of anaerobic organisms is ensured. Ampicillin is added to cover for *L. monocytogenes* in neonates, elderly and immunocompromised patients. If the patient is allergic to penicillin, chloramphenicol is used instead of cephalosporin and trimethoprim–sulfamethoxazole is the alternative to ampicillin. Nosocomial infections are treated with vancomycin and either ceftazidime or meropenem.

Current guidelines support the concurrent use of dexamethasone with antibiotic therapy in ABM. The host inflammatory response to bacterial insult may cause considerable brain injury, with bacterial lysis triggering the release of inflammatory cytokines. Steroids block this inflammatory cascade. Dexamethasone is given intravenously in a dose of 8–10 mg every 6 hours. It is started at the time of or just prior to commencing antibiotic therapy. In a large nationwide study, patients with pneumococcal meningitis, who were concurrently treated with steroids had reduced mortality, deafness and other neurological sequelae.[11] Once the organism is detected, steroids are continued only in those whose cultures have grown pneumococci.

Table 2: Specific antibiotic therapy for acute bacterial meningitis

Organism	*Antibiotics*
S. pneumonia • sensitive to penicillin • relative resistance • resistant to penicillin	 Penicillin G or ampicillin third generation cephalosporin third generation cephalosporin + vancomycin
N. meningitis	Penicillin G or ampicillin or extended spectrum cephalosporin
H. Influenzae • β-lactamase negative • β-lactamase positive	 Ampicillin third generation cephalosporin
L. monocytogenes	Ampicillin or penicillin G (alternative: trimethoprim–sulfamethoxazole)
Gram-negative bacilli	Third generation cephalosporin
Pseudomonas aeruginosa	Meropenem or cefepime
S. aureus	Vancomycin

If treatment is instituted without delay, rapid improvement is expected. Failure to observe this within 48–72 hours should prompt a review of the working diagnosis and a repeat CSF examination. Once the causative organism with its antibiotic sensitivity is identified by blood and CSF cultures, specific antibiotic therapy is initiated (Table 2). Parenteral antibiotics are given for 7 days in meningococcal and *H. influenzae* meningitis, 10–14 days for pneumococcal infection and 3–4 weeks for listerial and Gram-negative bacillary infections. The challenge in treating meningitis lies in not only eradicating the infection from the meninges, but also in locating and removing its source, so that the person is spared the ordeal of recurrent meningitis.

A high index of suspicion is required to diagnose TBM. Patients with fever, headache and stiff neck with a CSF lymphocytic pleocytosis and a mild to moderate decrease of glucose concentration (20–40 mg%) are usually started on anti-tuberculosis (TB) drugs. First line therapy usually consists of isoniazid, rifampicin, pyrazinamide and ethambutol with or without streptomycin injections. Steroids are started concomitantly, especially when CSF proteins are high or when CT or MRI shows thick basal exudates, hydrocephalus or vasculitic infarcts. A discussion on second-line drug therapy in multi-drug-resistant tuberculosis (MDR-TB) is beyond the scope of this chapter.

The treatment of viral meningitis is largely supportive as it is usually a self-limiting illness. There are, however, some exceptions. Enteroviral meningitis occurring in an immunocompromised host can be virulent and life-threatening. Pleconaril, a new antiviral agent effective against enteroviruses, can be given, though it is not freely available.[12] Sexually transmitted HSV-2 infection is treated with oral acyclovir (800 mg 5 times a day) or famciclovir (500 mg 3 times a day) or valacyclovir (1 g 3 times a week) for 2 weeks to prevent a recurrence of meningitis.

Complications and Prognosis

Cerebral edema with raised ICP commonly occurs in stuporous or comatose patients with acute meningitis. Along with the definitive treatment for meningitis outlined above, urgent measures to lower ICP must be instituted. They include hyperventilation, hyperosmolar therapy and, in refractory cases, barbiturate coma (for a more detailed account, please refer to the subchapter Raised Intracranial Pressure of chapter Neurological Problems. Hydrocephalus develops in about 8% of patients, especially those with tuberculous, fungal and listerial meningitis. It is managed with repeated LPs or by employing an external ventricular device. TBM also causes vasculitic strokes. Subdural empyema, brain abscess or venous sinus thrombosis may complicate meningitis associated with sinusitis or otitis media. Hyponatremia occurs either due to the syndrome of inadequate ADH secretion or salt wasting. Sensorineural hearing loss is a frequent and early complication of ABM. Seizures occur in 5–15% of patients with bacterial meningitis and should be treated with appropriate antiepileptic drugs. A continuous electroencephalography (EEG) monitoring helps to detect the occasional patient with nonconvulsive status epilepticus (SE). Septic shock and disseminated intravascular coagulation (DIC) are dreaded complications, more likely to occur with delayed diagnosis and treatment. Meningococcal meningitis rarely causes the Waterhouse-Friderichsen syndrome with adrenal failure and DIC.

Poor prognostic factors in ABM include age over 60 years, concomitant debilitating disease, low Glasgow coma scale (GCS) score on admission, presence of a focal neurological deficit and a low CSF cell count less than 1,000/mL.[2] Pneumococcal meningitis carries the highest mortality. Nearly 50% of survivors are left with significant disability such as developmental delay, cognitive impairment and epilepsy.[13]

ACUTE ENCEPHALITIS

Viral encephalitis is the most common cause of infective encephalitis. Several families of viruses are known to cause focal or diffuse inflammation of brain parenchyma. HSV-1 and VZV belonging to the herpes virus family are frequent causes of viral encephalitis worldwide, occurring throughout the year with no seasonal incidence. The JE virus and WNV belong to the flavivirus family, cause arthropod (mosquito)-borne disease and have a seasonal distribution. Cytomegalovirus (CMV), human herpes virus 6, EBV and enteroviruses cause encephalitis mainly in immunocompromised individuals. Rickettsial infections are caused by bacteria and transmitted by tick bite (Rocky Mountain Spotted Fever). Rabies is endemic in India due to the large number of stray, unvaccinated dogs. The causative organism remains unidentified in 40–50% of cases.

Clinical Considerations

Patients with acute encephalitis typically present with fever, headache and one or more of the following: confusion, behavioral change, decreased level of consciousness, new

onset seizures and focal neurologic deficits. The etiological organism can often be predicted on the basis of the season, area of residence, travel and contact with animals and immune status of the individual. Enteroviral (coxsackie and echovirus) and arboviral infections tend to peak during summer, while HSV and VZV occur throughout the year. A trip to India and Nepal increases the likelihood of JE, rabies and falciparum malaria. Travel to South America increases the risk of rabies, Eastern equine and Western equine encephalitis. Cases of JE tend to cluster in areas of close contact between humans and pigs. In areas of geographic prevalence, a history of tick bite may suggest kyasanur forest disease or Rocky Mountain Spotted Fever.

Some viruses cause well-defined clinical syndromes due to their predilection for specific brain regions. The flaviviruses (JE virus and WNV) predominantly affect the *basal ganglia,* producing parkinsonian features and dystonia. They also have an affinity for the anterior horn cells of spinal cord which causes an acute flaccid limb paralysis resembling poliomyelitis. Patients with HSV-1 encephalitis present with a *limbic encephalitis* with significant memory impairment, behavioral changes, confusion, word finding difficulty and seizures. A similar syndrome occurs in autoimmune encephalitis, mainly anti-NMDA (N-methyl D-aspartate) receptor encephalitis. As many as one-third of acute encephalitis cases in children are likely to be immune-mediated.[14] VZV produces a *vasculopathy* involving large and small vessels resulting in ischemic and hemorrhagic infarcts. VZV encephalitis often follows shingles, the classic dermatomal skin rash, but occurs in its absence as well. Cerebellar ataxia and myelopathy are its other neurological manifestations.[15]

Diagnostic Approach

A brain MRI is more sensitive than CT scan in visualizing the abnormalities of encephalitis. Basal ganglia, thalamic and brainstem lesions caused by JE virus and WNV are clearly demonstrated on MRI. T2-weighted and flair hyperintensities in the temporal lobes are a feature of HSV-1 encephalitis. In measles encephalitis, lesions are seen in the temporal and frontal cortical gyri. MRI can be normal in some patients. The CSF reveals a lymphocytic pleocytosis with mildly raised proteins and normal sugar. Identification of the causative agent is facilitated by CSF PCR techniques, CSF IgM antibody estimation and a fourfold increase in serum IgG titers of paired acute and convalescent serum samples.

Differential Diagnosis

Acute bacterial meningitis must always be considered in the differential diagnosis of acute encephalitis and, if doubt exists in the initial stages, empirical antibiotic therapy should be instituted. Patients with metabolic encephalopathy may also present with a similar clinical picture. Urgent blood levels of glucose, creatinine, ammonia, liver functions, calcium and thyroid along with serum and urine toxicology screen are ordered. In India, cerebral malaria and dengue must also be considered in a suspected case of encephalitis.

Autoimmune (AI) encephalitis and acute disseminated encephalomyelitis (ADEM) are close mimics of acute viral encephalitis. AI encephalitis presents as a limbic encephalitis and is often associated with paraneoplastic and other autoimmune disorders. Its onset is more gradual than its viral counterpart and it tends to progress over time. Anti-NMDA receptor encephalitis is the most common form of AI encephalitis and is usually associated with ovarian teratoma. In the California encephalitis project study, it was the most frequent cause of identified encephalitis, occurring mainly in young female patients, most of whom had no teratomas or other neoplasms.[16] These patients are treated with corticosteroids, plasma exchange, IVIg and, in some refractory cases, cyclophosphamide and rituximab. ADEM is an acute, immune-mediated demyelinating illness which usually follows a viral infection or immunization. The clinical picture resembles acute encephalitis. The presence of multifocal neurologic signs should make the physician suspect ADEM. MRI of brain shows large, asymmetric enhancing lesions involving the subcortical white matter and the gray-white junction of both cerebral hemispheres. Treatment consists of IV methylprednisolone. Plasma exchange and IVIg are alternative treatment options.

Management of Acute Encephalitis

Patients with acute encephalitis are often very ill with altered sensorium ranging from somnolence to deep coma. They require optimal critical care in the ICU. After IV access is secured, blood is drawn and sent for all investigations as discussed earlier. Empirical antibiotic therapy along with acyclovir is started without any delay. Seizures, if present, are treated with IV lorazepam followed by IV phenytoin or fosphenytoin. Many patients present with difficult to control SE. Continuous EEG monitoring ensures that nonconvulsive SE is not overlooked. Severe behavioral disturbance with psychosis and aggression require major tranquillizers like parenteral haloperidol. Raised ICP is often present and its management is described in the subchapter Raised Intracranial Pressure of Chapter Neurological Problems. Hyponatremia due to SIADH requires careful attention to fluid and electrolyte balance.

In contrast to bacterial meningitis, few antiviral drugs are available for use. Acyclovir is the drug of choice for HSV-1 encephalitis. The high suspicion of HSV encephalitis in all sporadic cases has led to its inevitable overuse. It is given in a dose of 10 mg/kg 8 hourly daily for 21 days. Nephrotoxicity due to deposition of drug crystals is avoided by controlling the rate of infusion and keeping the patient well hydrated. Acyclovir is also given in the same dose to patients with VZV encephalitis for a period of 14 days. Oral prednisolone (1 mg/kg daily for 5 days) is given to treat the inflammatory component of vasculitis in VZV infection. Alternatives to acyclovir in VZV encephalitis include ganciclovir, famciclovir

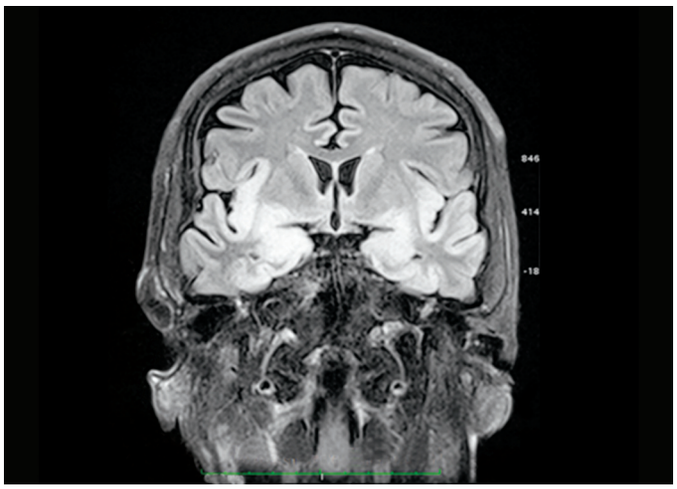


Fig. 9: Herpes simplex encephalitis: FLAIR coronal MR image I reveals symmetric restricted diffusion in insular cortex and frontal gyri due to herpes simplex encephalitis

and valacyclovir. Acyclovir has not shown any benefit in EBV encephalitis. Ganciclovir (5 mg/kg 12 hourly for 2–3 weeks) is used to treat CMV encephalitis. Foscarnet is used as an alternative agent in a dose of 60 mg/kg every 8 hours for 2–3 weeks.[17] The antiviral drug pleconaril has shown modest benefit in enteroviral infections.

HERPES SIMPLEX ENCEPHALITIS

Herpes simplex virus 1 accounts for 90% of cases in adults. It occurs at any age and affects men and women equally. It is a focal necrotizing, hemorrhagic encephalitis with a predilection for the temporal lobes, orbitofrontal cortex and cingulate gyrus. Besides the usual symptoms of headache, fever and altered mental state, patients frequently experience seizures with olfactory or gustatory hallucinations or déjà vu phenomena. Other features of temporal lobe dysfunction include aphasia, inability to store and recall new information and upper quadrant visual field defects.[18] Occipital lobe or brainstem affection without temporal lobe involvement uncommonly occurs.

The CSF shows a lymphocytic pleocytosis of 50 or more cells per mL, mildly elevated proteins and normal sugar. Presence of RBCs or xanthochromia is due to the hemorrhagic nature of this encephalitis. MRI of brain shows T2-weighted, flair and diffusion-weighted hyperintensities over the medial temporal lobes in 90% of patients within 48 hours of onset. The insula, orbitofrontal cortex and cingulate gyrus are also affected. The EEG often shows periodic lateralized epileptic discharges. The diagnosis is established by the detection of HSV DNA by PCR technique in CSF. Its diagnostic accuracy is 98%. It tests positive within 72 hours of symptom onset. A serum to CSF HSV IgG ratio of less than 20:1 indicates intrathecal antibody synthesis and is also diagnostic. However, it takes 8 days for antibodies to be detected in CSF. The prompt administration of acyclovir has reduced the mortality from more than 70% to 14%.[19] About 30% of patients are left with permanent sequelae like seizures, aphasia and cognitive impairment (Fig. 9).

JAPANESE ENCEPHALITIS

Japanese encephalitis is the most common cause of arboviral encephalitis worldwide. It is caused by a *Flavivirus* which is transmitted by the bite of the *Culex* mosquito. Although JE virus transmission continues throughout the year in the tropics, seasonal epidemics occur during the rainy season when the mosquito density is maximum. JE must be suspected in any patient with recent travel to Asia and presenting with meningitis, encephalitis or acute flaccid paralysis. JE patients commonly have parkinsonian features with masked facies, tremors, akinesia and rigidity. A fixed limb and axial dystonia along with chorea and myoclonus may also be seen. Affection of the anterior horn cells causes flaccid limb paralysis resembling poliomyelitis. MRI scans confirm the predominant involvement of the basal ganglia, thalami and brainstem. Bilateral thalamic involvement in a patient with encephalitis residing in an endemic area strongly suggests JE. The detection of JE IgM antibodies by ELISA in CSF is diagnostic of JE. Treatment is by supportive measures only. JE carries a 25% mortality risk. About 50% of survivors have severe cognitive impairment, focal weakness, seizures and movement disorders.

RABIES

Rabies encephalitis remains a significant health problem in developing countries where dogs are not routinely vaccinated. In the West, rabies is associated with bites from bats, raccoons and foxes. It is caused by the *Lyssavirus* and its incubation period is usually a few months. It presents in two ways: (1) *Encephalitic form*—patients present with pharyngeal spasms, hydrophobia, hyperactivity and hallucinations which rapidly progress to worsening encephalopathy, limb paralysis, coma and death. (2) *Paralytic form*—initial presentation is with rapidly progressive quadriparesis which then leads to encephalopathy, coma and death. Rabies carries a nearly 100% mortality. Only a handful of surviving cases have been reported in world literature.[20] Postexposure rabies prophylaxis for nonimmunized individuals consists of five doses of human diploid cell vaccine along with rabies immunoglobulin (20 IU/kg).

CEREBRAL MALARIA

A mosquito-borne illness caused by a protozoan parasite *Plasmodium falciparum*, malaria is endemic in Africa, South America and Asia. Patients with cerebral malaria present with fever with chills and rigors, headache, malaise, vomiting, diarrhea, myalgia and a decreased level of arousal. Seizures are more frequent in children (80% vs 15–20% of adults). A sixth nerve palsy, ocular bobbing, bruxism, ataxia, tremors, cortical blindness and deceorticate/decerebrate rigidity also occur, though less commonly. The disease

tends to be more severe in children and pregnant women. Cerebral malaria must be considered in any patient with a febrile illness and encephalopathy residing in or returning from an endemic area for malaria. Diagnosis is based on an impaired level of consciousness, presence of parasitemia on a peripheral blood film and exclusion of other causes of encephalopathy. A positive falciparum antigen and elevated lactate dehydrogenase (LDH) also help to diagnose malaria.[21] The CSF may be normal or show mildly elevated proteins and cells. MRI scan of brain shows white matter hyperintensities, cortical infarcts or cerebral edema. Hypoglycemia, severe anemia, acidosis and thrombocytopenia are common complications of cerebral malaria. Multiorgan dysfunction in the form of renal failure, jaundice and acute respiratory distress syndrome carries a poor prognosis. Cerebral malaria is a medical emergency. The aim is to rapidly reduce parasitemia with effective drug therapy and carefully manage the various complications that arise. Due to widespread resistance to chloroquine, the drugs of choice are intravenous quinine or parenteral artemether compounds. Quinine can cause hypoglycemia which may go undetected in an unconscious patient unless suspected.

DENGUE FEVER

Dengue is caused by a *Flavivirus* which is transmitted by the *Aedes aegypti* mosquito. Patients present with high fever, severe myalgia and arthralgia (breakbone fever) and a petechial or macular rash. Thrombocytopenia commonly occurs. Neurological manifestations are uncommon, but when they occur, they indicate a poor prognosis. They include meningoencephalitis, coma, intracerebral hemorrhage, transverse myelitis and a Guillain-Barré-like syndrome.[22] Laboratory diagnosis of dengue infection is made by IgM ELISA in blood or CSF. The NS1 monoclonal antibody is an ELISA-based test that enables early diagnosis to be made. There is no specific antiviral therapy for dengue.

NEUROLOGICAL INFECTIONS IN HIV

Neurosyphillis occurs in HIV patients, especially in those with a low CD4 count and high viral load. The primary infection is caused by the spirochete *Treponema pallidum.* Meningovascular syphilis is the common form of neurosyphilis. Patients develop aseptic meningitis with cranial nerve involvement, in particular, optic neuritis. A CSF pleocytosis with normal sugar and mildly elevated proteins is seen. There is also a frequent occurrence of brainstem and cerebral lacunar infarcts due to the propensity of the organism to affect small arterioles. Brain parenchymal changes similar to HSV encephalitis may be seen on MRI in these patients. The diagnosis requires a positive CSF VDRL and fluorescent treponemal antibody (FTA) absorption test. Aqueous crystalline penicillin (3 million units IV every 4 hours for 14 days) is the mainstay of treatment.

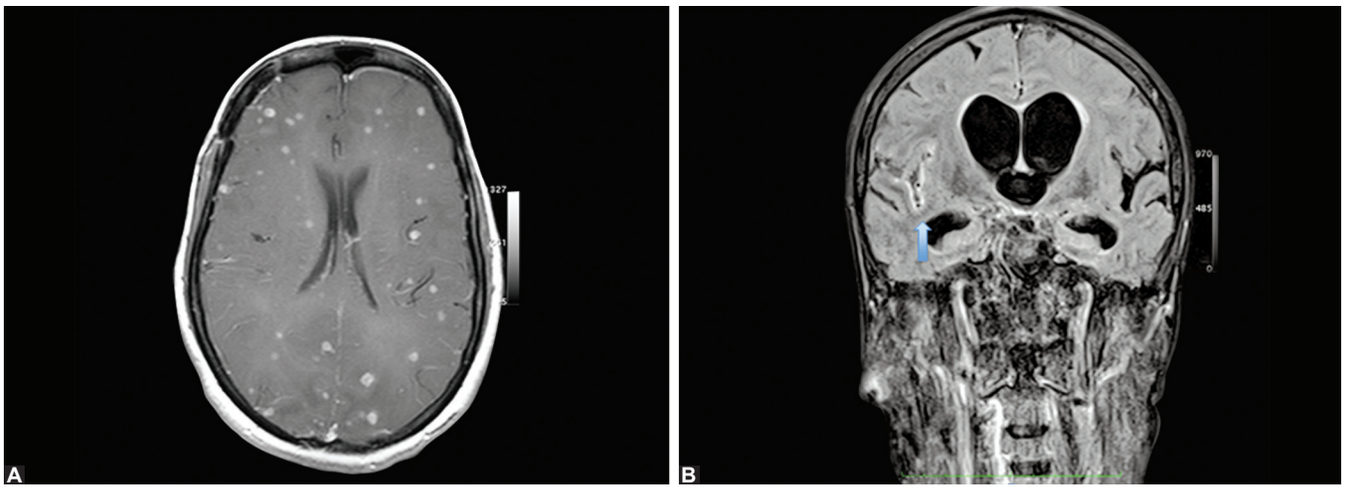
Cryptococcal meningitis is the most common CNS fungal infection in HIV, typically occurring when the CD4 count falls to less than 100 cells/mm^3. It occurs in immunocompetent people as well. The causative organism is *Cryptococcus neoformans*, an encapsulated yeast. It usually causes a subacute to chronic meningitis, but sometimes it can present fulminantly. Patients develop hydrocephalus, vasculitic strokes and cranial nerve palsies (usually II and VIII nerves). A striking feature of cryptococcal meningitis is the significantly raised ICP it causes with papilledema and markedly elevated CSF pressure in excess of 40 cm of water. In such patients, repeated (sometimes daily) LPs with CSF drainage help. A positive CSF culture with cryptococcal antigen or India ink stain clinches the diagnosis.

Treatment of cryptococcal meningitis is initiated with amphotericin (0.7–1 mg/kg per day) or its lipophilic analogue, ambisome (5 mg/kg per day) along with flucytosine (100 mg/kg per day) for a minimum of 15 days. Amphotericin can cause nephroxicity, hepatitis and bone marrow suppression. Fluconazole in a high dose of 800 mg/day can be used instead of flucytosine, given the latter's toxicity and its unavailability in developing countries. There is no role for steroids or acetazolamide in the treatment of raised ICP.[23] This induction phase is followed by a consolidation phase with oral fluconazole 400 mg/day for 10 weeks and a maintenance phase with oral fluconazole at 200 mg/day. Immunocompromised patients may require 6–12 months of treatment till CSF becomes sterile.

Tuberculous meningitis is the most common cause of death worldwide in HIV patients. A sharp increase in incidence of TBM has occurred in the wake of the global AIDS epidemic. The clinical presentation is that of subacute basal meningitis with the frequent occurrence of cranial nerve palsies, stroke and hydrocephalus. CSF in HIV patients is similar to non-HIV patients except that pleocytosis is less and proteins are not as markedly elevated. Neuropathological examination of the TBM brain in seropositive cases reveals scanty basal exudates compared to seronegative patients. The brain parenchyma is found teeming with acid-fast bacilli in them. These findings reflect the severely impaired cell-mediated immunity in seropositive cases with resultant unlimited spread of the tubercle bacilli.[24] MDR-TB must be suspected in an HIV-infected TBM patient and treated accordingly (Figs 10A and B).

Cytomegalovirus encephalitis is an opportunistic viral infection which usually occurs when CD4 counts fall to less than 50 cells/mm^3. Patients present with a subacute progressive encephalopathy with impaired memory, behavioral disorder, gait disturbance and headache. The CSF may be normal or show mild lymphocytic pleocytosis with elevated proteins. A positive CSF CMV PCR with HIV is diagnostic. CMV also frequently affects the retina, GI tract, lungs and liver. Patients are treated with IV ganciclovir or foscarnet or once-weekly cidofovir.

Toxoplasmosis is the most common cause of focal cerebral mass lesion in HIV. It is caused by *Toxoplasma gondi,* an obligate intracellular protozoan parasite. This organism mainly produces intraparenchymal abscesses. The clinical



Figs 10A and B: (A) Tuberculomas: Postcontrast MRI of brain reveals multiple ring and nodular enhancing lesions representing tuberculomas; (B) TBM with hydrocephalous: Postcontrast MRI of brain reveals dilated ventricles with periventricular lucencies due to transependymal seepage of CSF. Note basal exudates enhancing in right sylvian fissure

picture usually evolves over days to weeks with about half the patients complaining of headache, fever and lethargy.[25] Focal deficits like hemiparesis and ataxia reflect the location of the toxoplasma abscesses. CT or MRI scan shows single or multiple round, ring or nodular enhancing lesions mainly in the basal ganglia or deep white matter. The CSF ELISA test for toxoplasmosis is both specific and sensitive. However, a CSF sample is not always possible to obtain as the large mass lesion makes LP a risky procedure. A presumptive diagnosis is then made by response to a therapeutic trial. Treatment consists of a combination of pyrimethamine 75–100 mg/day and sulfadiazine 1.5 g four times a day for 3–4 weeks. Clinical benefit usually occurs in 1–2 weeks, with radiographic improvement taking 2–3 weeks. A stereotactic aspiration/biopsy is considered if there is no response to treatment or if the patient has a low risk for toxoplasmosis.

Progressive multifocal leukoencephalopthy (PML) is a subacute demyelinating CNS disease caused by the John Cunningham (JC) virus, occurring in about 5% of patients with AIDS. Progressive focal neurologic deficits like hemiparesis, ataxia and visual disturbance are accompanied by cognitive impairment and altered sensorium. The MRI shows asymmetric, multifocal, subcortical nonenhancing white matter lesions predominantly in the parieto-occipital and frontal regions. There is no effective therapy for PML. Initiation of ART improves some patients.

BRAIN ABSCESS

It is a localized collection of pus in the brain parenchyma. It commonly occurs due to contiguous spread of infection from neighboring structures like paranasal sinus, middle ear or mastoid. A disruption of the dura, as occurs in penetrating head injury and postneurosurgical procedures, also predisposes to brain abscess. Multiple abscesses also develop due to hematogenous spread of infection from a distant source as in infective endocarditis, congenital cyanotic heart disease and pulmonary diseases. The cause is not identified in 30% of cases. Brain abscess is usually polymicrobial in nature. *S. aureus* and Gram-negative bacilli are the most common pathogens following penetrating head injury or neurosurgery. Similar bacteria along with anaerobes are linked to paranasal sinusitis, otitis media and mastoiditis. *Toxoplasma*, *Nocardia*, *Listeria* and *Aspergillus* are implicated in immunocompromised patients.

An abscess usually begins as a localized area of cerebritis which later evolves into an encapsulated focus of infection. Clinical features of headache and fever are followed by focal neurological deficits like hemiparesis or ataxia depending on the location of the abscess. Features of raised ICP occur if the abscess is large. An LP is usually contraindicated due to the spaceoccupying effect of the lesion. Blood cultures are ordered as soon as possible prior to starting antibiotic therapy. A CT or MRI scan shows a single or multiple ring-enhancing lesion/s with central low density and surrounding edema.

Empirical antibiotic therapy is instituted as soon as possible. Vancomycin, ceftriaxone (or ceftazidime) and metronidazole are given. If pseudomonas is suspected, vancomycin and meropenem are used. Aminoglycosides, erythromycin and tetracyclines are avoided as they penetrate the blood-brain barrier poorly. Parenteral antibiotics are continued for 6–8 weeks depending on the clinical and radiographic response. Stereotactic CT-guided aspiration or surgical excision of the abscess is recommended if it is more than 2.5 cm in size.[26] This also enables a definitive microbiologic diagnosis to be made. Medical treatment alone is indicated when the abscess is less than 2 cm in diameter, if cerebritis is present or if the abscesses are multiple and surgically inaccessible. An initial short course of steroids is considered only if significant cerebral edema exists.

SUBDURAL EMPYEMA AND CRANIAL EPIDURAL ABSCESS

Subdural empyema refers to the presence of purulent infection over the cerebral convexity between the dura mater and arachnoid membranes. A cranial epidural abscess occupies the space between the dura mater and the inner skull table. The sources of infection, incriminating organisms and empirical therapy for both these conditions are nearly the same as for brain abscess discussed above. Subdural empyema is most likely to occur as a consequence of frontal sinus infection, while a cranial epidural abscess is often associated with osteomyelitis of the skull. Clinical features are similar to those of ABM with acute onset of fever, headache and rapid deterioration of sensorium. MRI of the brain is the imaging modality of choice for both these conditions. Urgent surgical drainage of empyema and evacuation of abscess is indicated. Simultaneously, empirical antibiotic therapy is instituted as mentioned in brain abscess. Parenteral antibiotics are usually given for 3–6 weeks, and followed by 3 weeks of oral therapy. Life-threatening complications include cortical vein or dural sinus thrombosis with hemorrhagic infarction, brain abscess and cranial osteomyelitis. Prognosis is better for cranial epidural abscess than for subdural empyema as the infection tends to be more localized.

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E. STATUS EPILEPTICUS

Jimmy Lalkaka, BS Singhal

INTRODUCTION

Status epilepticus (SE) is a common neurological emergency encountered in hospital practice. It can be broadly classified into two groups, convulsive status epilepticus (CSE) with persistent motor activity and nonconvulsive status epilepticus (NCSE) with a lack of involuntary motor phenomena. Generalized convulsive status epilepticus is the commonest form of CSE. Unless specified otherwise, SE will imply generalized convulsive SE for the purpose of this chapter.

DEFINITIONS

Traditionally, SE has been defined as either a continuous motor seizure lasting 30 minutes or more or two or more seizures without regaining full consciousness between them. The newer operational definition of SE which is favored by most neurologists is that it denotes any seizure lasting more than 5 minutes, or two or more seizures with incomplete recovery of consciousness between them.[1] This definition captures the essence of SE which is that seizures become prolonged or repetitive because of a failure of normal seizure terminating mechanisms. Most seizures terminate spontaneously within 3 minutes of onset.[2] If they persist for more than 5 minutes, they are unlikely to self-terminate and, hence, the need for urgent intervention. Refractory status epilepticus (RSE) refers to SE in which seizures persist despite adequate first and second line antiepileptic drug (AED) therapy. Of those who develop SE, about a quarter progress to RSE.[3] NCSE is characterized by altered sensorium for 30 minutes or more with no convulsive body movements and EEG evidence of ongoing epileptic activity.[4] This condition is underrecognized and often misdiagnosed. It accounts for about 25% of SE cases. About 8% of patients with unexplained coma have NCSE.[5] So, it must be considered in any patient with an unclear cause of acute coma or altered sensorium.

ETIOLOGY OF STATUS EPILEPTICUS

Status epilepticus often occurs in the setting of acute and remote symptomatic seizures. Common causes include strokes (acute and chronic), CNS infections (meningoencephalitis, cerebral malaria), head injury, hypoxic encephalopathy, brain tumor, metabolic derangements (hyponatremia, hypoglycemia, hypocalcemia, hepatic and renal disturbances) and alcohol and drug intoxication.

Status epilepticus also commonly occurs in patients with prior epilepsy. In them, SE is often precipitated by AED withdrawal or poor drug compliance resulting in low AED levels. Many Indian patients who undertake fasts for religious purposes also unfortunately stop their AEDs during this period. Keeping awake for most of the night causes sleep deprivation which can trigger SE in susceptible individuals. Fever and use of drugs like penicillin, quinolones and chloroquine can also aggravate seizures. SE can occur as the initial manifestation of epilepsy about 12% of the time, especially in children.[6] No clear etiology can be identified in about 20% of cases.[7]

Some conditions are more likely to cause RSE than others. Encephalitis (herpes simplex virus, Japanese B and paraneoplastic autoimmune encephalitis) and hypoxic encephalopathy are more likely to cause RSE than AED withdrawal or alcohol-related SE. Autoimmune encephalitis is being increasingly recognized as an important cause of RSE.[8] Of the several antibodies linked to RSE, antibodies to N-Methyl D-Aspartate (NMDA) receptors have a particularly close association with RSE of unknown etiology.[9] NMDA receptor encephalitis often presents with acute psychiatric and cognitive symptoms before seizures occur. Movement disorders, especially choreoathetosis, and autonomic disturbances usually occur at a later stage. NMDA antibodies are commonly associated with neoplasms, mainly ovarian carcinoma. If detected, removal of the neoplasm could result in resolution of SE.

NEUROLOGICAL COMPLICATIONS OF STATUS EPILEPTICUS

Direct neuronal injury occurs as a result of continuous seizure activity. The severity of damage depends on the duration of seizure activity and the etiology of SE (encephalitis and cerebral hypoxia cause more neuronal damage than AED withdrawal seizures). Certain regions of the brain are particularly vulnerable to the effects of SE. They are the hippocampus, amygdala, pyramidal cells of cerebellum and thalamus. These regions have high excitatory amino acid receptor activity. Injury to these areas causes memory and cognitive impairment, gait imbalance and disturbance of affect. Besides excitotoxic injury, hypoxia, ischemia and metabolic disturbances cause diffuse cerebral edema and elevated intracranial pressure. Development of epileptogenic foci during SE increases the risk of subsequent epilepsy.

SYSTEMIC COMPLICATIONS OF STATUS EPILEPTICUS

The early stage of SE is called the compensated stage. It is marked by a spurt in the level of circulating catecholamines with sympathetic overdrive. This causes hypertension, tachycardia and hyperglycemia. Cerebral blood flow is markedly increased to compensate for the phenomenally raised cerebral metabolic rate in SE. Cardiac arrhythmias also occur at this stage. Due to continuous muscle activity, the core

body temperature steadily rises, resulting in hyperthermia and neuronal damage, particularly to the cerebellum. Prolonged SE also causes muscle breakdown and rhabdomyolysis, which lead to acute renal failure. Acidosis due to lactic acid production also occurs.

If SE continues, a late phase of decompensation is reached, in which hypotension and hypoxia occur. AEDs aggravate hypotension, particularly if general anesthetics are used. Cerebral perfusion and blood flow decrease alarmingly due to failure of cerebral autoregulation. Hypoglycemia ensues because of depletion of glycogen stores. Pulmonary edema, if present during this stage, worsens the outcome of SE.

MEDICAL MANAGEMENT OF STATUS EPILEPTICUS

Successful management of SE requires adequate and effective treatment in the appropriate window period. So a pre-established time-based plan of action must be in place in order to terminate the seizure and ensure a satisfactory outcome with minimal complications.

Initial Stage of Status Epilepticus (0–10 Minutes)

Benzodiazepines (BDZ) are universally accepted as the first line AED in SE. Intravenous (IV) lorazepam 0.1 mg/kg is given as a bolus over 1–2 minutes (maximum 4 mg). If seizures continue after 5 minutes, the above dose can be repeated. Alternative drugs are intravenous (IV) diazepam 0.2 mg/kg over 1 minute (maximum 10 mg) and IV midazolam 0.1–0.2 mg/kg. All three drugs have proven efficacy in terminating seizures. They are effective about 65% of the time in terminating SE, provided they are given early. Lorazepam is the preferred drug. It has less risk of seizure recurrence because of its prolonged drug action up to 12 hours and a decreased volume of distribution. Diazepam and midazolam have a very rapid onset of action, but they tend to redistribute from cerebral tissue to larger peripheral lipid tissue. Hence, their action is relatively short lived.

If seizures occur at home and IV access is not available, midazolam can be given by the intranasal, buccal or intramuscular route. Rectal diazepam (0.5 mg/kg in children and 20 mg in adults) can also be administered at home. Buccal midazolam was found to be superior to rectal diazepam in stopping seizures in children and was easier to administer.[10] Interestingly, a recent study of drug administration by paramedics in the early stage of SE showed that intramuscular midozolam was more beneficial than IV lorazepam because of the speed with which it could be administered.[11] Bioavailability after an intramuscular injection is 80–100% and peak levels are attained in 25 minutes. Prompt pre-hospital administration of BDZ is clearly beneficial in terminating SE early and ensuring a better outcome.

All patients with SE should be treated in the intensive care unit (ICU) of a well-equipped hospital. The first step is to ensure adequate airway, breathing and circulation status. Nasal oxygen is started. Intravenous access is ensured. Finger prick blood sugar estimation is done. Blood is collected for urgent hematocrit, electrolytes, liver and renal functions, calcium, magnesium, AED levels, arterial blood gases (ABGs) and toxicology screen. About 50 cc of 50% glucose along with 100 mg of thiamine IV are given to take care of any hypoglycemic or alcohol related disturbance. IV lorazepam or diazepam is given as mentioned earlier.

Established Status (10–30 Minutes)

In most cases, a second line, longer acting AED is used concurrently with BDZ. The second line AED is usually phenytoin or fosphenytoin. Phenytoin is given as a bolus of 15–20 mg/kg in about 50–100 cc of normal saline at a rate not more than 50 mg/minute. Regrettably, lower doses are often given and this is one of the common reasons for uncontrolled SE. Phenytoin can sometimes cause hypotension and cardiac arrhythmias. So constant monitoring of BP and ECG is essential during an infusion. The toxicity of phenytoin is more dependent on the rate of infusion than on the total dose. Hence, it is advisable to infuse it at a slower rate (20–30 mg/minute) in the elderly and those with conduction defects. Being highly alkaline, phenytoin can produce chemical phlebitis. Extravasation of phenytoin into subcutaneous tissue may cause soft tissue necrosis, thrombosis and distal limb ischemia, the so-called "purple glove syndrome". So after an infusion, the vein should be flushed with normal saline.

Fosphenytoin is a prodrug of phenytoin. As it is water-soluble with a significantly lower pH than phenytoin, tissue necrosis does not occur if it extravagates into subcutaneous spaces. It is infused using standard IV solutions, whereas phenytoin cannot be given in dextrose-containing fluids as it precipitates out. It also produces significantly less hypotension and so can be infused more rapidly at a rate of 150 mg/minute. The dose is 18–20 mg/kg phenytoin equivalents.

Sodium valproate can be used as an alternative to phenytoin or fosphenytoin. It is as effective as phenytoin in controlling SE. The advantage of valproate is that it has no cardiovascular effects, but it can rarely cause hyperammonemia, hepatic disturbance and pancreatitis. Usually, an IV bolus of 1 g (20–40 mg/kg) over 15–20 minutes is given. If seizures continue, additional doses of 500 mg of valproate or 5 mg/kg of phenytoin or fosphenytoin can be given.

Intravenous phenobarbitone is another alternative drug that can be used at this stage in patients who are allergic to phenytoin or in whom phenytoin has failed to control SE. It has a rapid onset of action and a prolonged anticonvulsant effect. However, its main disadvantages are that it causes sedation, hypotension and respiratory depression, which require prior intubation and ventilation. The recommended loading dose is 10–20 mg/kg given at a rate of 60 mg/minute.

Levetiracetam, one of the newer AEDs, is increasingly being used as an alternative to valproate or phenytoin. Its advantages are that it is water soluble, easy to administer and has very few side effects. It is given in a loading dose of 50 mg/kg over 15 minutes at a rate of 100 mg/minute (maximum 4 g). It can be given to elderly patients with medical comorbidities

and also when phenytoin is contraindicated.[12] Large randomized trials for establishing the efficacy of levetiracetam in SE are lacking. An observational study found levetiracetam to be inferior to valproate as a second line drug for SE.[13] Lacosamide is another new AED reported to have efficacy in nonrefractory SE. It is given in a dose of 300 mg IV over 30 minutes. It does not cause respiratory depression or cardiovascular disturbance. However, more data is needed before it can be routinely prescribed in SE. Given the present state of knowledge, phenytoin, fosphenytoin or valproate would still be the preferred second line AEDs in SE.

Along with drug therapy, patients with established SE must be carefully monitored for any systemic complications. Acidosis must be appropriately treated, blood oxygen levels maintained and electrolyte and renal parameters closely monitored. Hyponatremia may precipitate or aggravate SE. Hyperthermia must be reversed with appropriate cooling methods and antipyretics and a very high BP must be reduced with appropriate antihypertensives. Hypotension, if present, is treated with IV fluids and pressor agents, if required.

A CT or MRI scan of the brain should be done, especially in non-epileptic patients. However, neuroimaging must not delay AED treatment. Also, patients must be hemodynamically stable and not get a seizure during the CT or MRI scan. SE can cause hippocampal edema and posterior reversible leukoencephalopathy which are detected on MRI scan.[14] An urgent lumbar puncture (LP) must be performed in febrile patients with SE who have no prior history of epilepsy to rule out meningeoencephalitis. If LP is not safe because of ongoing SE, empirical antibiotics with or without acyclovir and antimalarials must be started immediately. CSF pleocytosis has been described within 24 hours of SE onset without any evidence of acute infection.[15]

Refractory Status Epilepticus (>30–60 Minutes)

As mentioned earlier, RSE refers to SE in which seizures continue despite adequate doses of first and second line AEDs. Failure of bolus of two AEDs to control seizures makes it unlikely that patients will respond to a third bolus dose. So, a continuous IV infusion is needed at this stage. RSE must be managed in the ICU and a continuous EEG monitoring is mandatory because many patients continue to have EEG seizure activity with only subtle clinical manifestations like focal twitches and few myoclonic jerks. Infusions of midazolam or anesthetic agents like propofol, pentobarbital or thiopental are given at this stage. Patients must be on ventilator support as these agents (especially anesthetics) cause respiratory depression. Midazolam is given as a bolus of 0.2 mg/kg (maximum 10 mg) over 2 minutes and then as a continuous infusion at a rate of 0.1–0.4 mg/kg per hour to stop clinical attacks and correct abnormal EEG activity. Hypotension is the main side effect of midazolam, which is treated by reducing the infusion rate or judiciously using pressor agents. MDZ has occasionally been given in very high doses of up to 2.9 mg/kg per hour to suppress EEG ictal activity. Tachyphylaxis can occur with midazolam infusion, increasing the risk of breakthrough seizures.

Propofol is commonly used in RSE. It is a gamma amino butyric acid-A (GABA-A) agonist with rapid onset of action within 3 minutes and easy reversibility. This short elimination half-life ensures rapid awakening within 10–15 minutes after stopping the drip. Its mode of action also includes inhibition of NMDA receptors and modulation of calcium influx. It is given as an IV bolus of 1–2 mg/kg over 5 minutes, followed by a maintenance infusion at 2–10 mg/kg per hour. Respiratory depression and hypotension are common side effects. The rate of infusion is adjusted either to terminate EEG and clinical seizure activity or to achieve a burst-suppression pattern on EEG. The latter is referred to as the "coma phase" with continuous EEG monitoring. Barbiturates like pentobarbital or thiopental in bolus doses followed by infusion are used as alternative anesthetic agents in RSE. Their mode and duration of administration are similar to propofol with the aim of maintaining burst-suppression on EEG. The barbiturates also help to lower ICP which is invariably elevated at this stage. Efficacy and mortality figures are more or less similar for midazolam, propofol and barbiturate infusions.[16] There are no clear guidelines as to which agent should be used first.

The anesthetic infusion is continued for about 12–24 hours after the last seizure. This is followed by the weaning phase in which the infusion rate is slowly reduced every 3 hours. During weaning, high therapeutic levels of phenytoin (18–30 mg/L) or valproate (70–120 mg/L) are maintained to prevent recurrent seizures during taper. The weaning process usually continues over 6–24 hours with continuous EEG monitoring to detect any seizure recurrence. If there is a recurrence of clinical or electrical seizure, then the anesthetic infusion drip is restarted and the whole process repeated. About one-third of patients with RSE will have seizures within 5 days of tapering the anesthetic medication. This is referred to as malignant SE.[17] Prolonged propofol infusion in a dose greater than 5 mg/kg per hour for more than 48 hours can cause the propofol infusion syndrome with significantly elevated creatine kinase (CK) (>2000 units/L), triglycerides (>500 mg%) and lactic acid (>2.5 mmoL/L) and low bicarbonate levels (<20 mmoL/L). Therefore, the propofol dose must not exceed 5 mg/kg per hour if the infusion is to be continued for more than 48 hours.

Other anesthetic agents like isoflurane inhalation (0.8–2%) and ketamine infusion (up to 5 mg/kg per hour) have on rare occasions been used when all the above drugs have failed to control seizures in RSE and malignant SE. Anesthesiology assistance is required during their administration. Ketamine may offer specific advantages over the other drugs in RSE.[18] It induces hypertension which may help to combat the hypotension which can occur in RSE.

Among the newer AEDs, topiramate and levetiracetam have shown efficacy in some cases of RSE. Topiramate is rapidly titrated and given in a high dose of 150–800 mg twice a day through nasogastric tube.[19] It is a carbonic anhydrase inhibitor and may cause acidosis. It should not be combined with propofol as this combination may aggravate acidosis.

Levetiracetam is given either IV at 20–30 mg/kg at 5 mg/kg per minute or orally in a dose of 1,500–3,000 mg through nasogastric tube.[20] The calcium channel blocker verapamil (120 mg/day) has also shown benefit in the occasional patient with RSE.[21]

Immunosuppressive therapy should be considered in all cases of RSE due to encephalitic illness of unknown cause as there is a high probability of autoimmune encephalitis (especially NMDA type). IV methylprednisolone 1 gm daily for 3–5 days should be given. If the drug fails to show benefit, IV immunoglobulins or plasma exchange should be tried. Rituximab and cyclophosphamide have also been successfully used in autoimmune SE in few cases (Table 3).

SUPER-REFRACTORY STATUS EPILEPTICUS

Status epilepticus that continues for more than 24 hours after the onset of anesthetic infusions is called super-refractory SE. If immune modulation has not been tried, it must be considered at this stage. A variety of alternative therapies have been suggested for this stage, but they are all either anecdotal case reports or small case series. They include electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), hypothermia and resective surgery.[22]

MAINTENANCE THERAPY

After the seizures have been successfully controlled, it is essential to continue maintenance therapy with appropriate AEDs to prevent seizure recurrence. Generally, the same drugs used to control SE like phenytoin or valproate are continued. Doses of these drugs are adjusted to maintain their blood levels in the normal therapeutic range. For patients receiving phenytoin and who are on nasogastric tube, it is preferable to continue IV dosing as a dramatic decline (about 70%) in absorption of phenytoin occurs when it is crushed and given through the tube.[23]

In critically ill patients who are on phenytoin and valproate, the free phenytoin level is three times higher than the expected level. So even a mildly low serum phenytoin level (8–10 mg) may suffice to prevent seizures. Drug interaction between valproate and the broad spectrum antibiotic meropenem causes a significant reduction in valproate levels.[24]

MANAGEMENT OF NONCONVULSIVE STATUS EPILEPTICUS

Nonconvulsive status epilepticus accounts for about 25% of SE cases. When the diagnosis is in doubt, a benzodiazepine

Table 3: Management of convulsive SE in adults

Time window (minutes)	*Medication*	*Medical measures*
0–10	IV lorazepam • 0.1 mg/kg bolus (maximum 4 mg) If seizure continues, repeat dose after 5 minutes Alternative drugs— • IV diazepam 0.2 mg/kg • IV midazolam 0.1–0.2 mg/kg If seizure outside hospital, no IV access: rectal diazepam 20 mg or midazolam 10 mg IM or intranasal or buccal	Secure airway Nasal oxygen Establish IV access Check finger prick blood sugar Collect blood for hematocrit, biochemistry AED level, ABG, toxicology screen Give IV 50 cc 50% glucose + 100 mg thiamine
10–30	IV phenytoin 15–20 mg/kg loading dose, rate not more than 50 mg/min or IV fosphenytoin 18–20 mg PE/kg at 150 mg/min or IV sodium valproate 20–40 mg/kg over 15–20 minutes Alternative drugs— IV levetiracetam 50 mg/kg or IV lacosamide 300 mg If seizure continues: repeat phenytoin/fosphenytoin 5 mg/kg or valproate 500 mg or IV phenobarbitone 10–20 mg/kg	Identify and treat medical complications Correct hyponatremia and acidosis If fever, use antipyretics and appropriate cooling methods Keep BP under control CT/MRI and CSF, if deemed necessary and safe Alert the anesthetist
30–60 Refractory SE	IV midazolam 0.2 mg/kg (maximum 10 mg), then infuse at 0.1–0.4 mg/kg per hour or IV propofol 1–2 mg/kg over 5 minutes; then infuse at 2–10 mg/kg per hour or IV thiopental sodium 3–5 mg/kg, then infuse at 3–5 mg/kg per hour or IV pentobarbitone 5 mg/kg at 25 mg/min, then infuse at 0.5–5 mg/kg per hour If suspected auto-immune encephalitis, IV methylprednisolone or IVIG or plasma exchange	Patient must be intubated and ventilated Continuous EEG monitoring Infusion must be titrated to maintain burst suppression pattern on EEG Closely monitor for hypotension Vasopressor therapy, if required Identify and treat complications Including hyperthermia and acidosis

trial is suggested. The patient is given sequential small doses of midazolam at 1 mg per dose. After each dose, clinical and EEG parameters are checked. The trial is stopped if any of the following occurs: (1) persistent resolution of EEG pattern; (2) definite clinical improvement; (3) respiratory depression or hypotension and (4) maximal permissible dose is reached (0.2 mg/kg). The test is reported positive if the ictal EEG pattern disappears and either the clinical state improves or a normal EEG pattern with posterior dominant alpha rhythm appears. The test is considered equivocal if the EEG improves but the patient does not. Treatment of NCSE is generally similar to that of generalized SE. However, mortality and morbidity figures are less in NCSE. So intubation and anesthetic drugs like propofol and barbiturates are generally avoided.

PROGNOSIS AND OUTCOME OF STATUS EPILEPTICUS

Status epilepticus is associated with high mortality rates of 15–22%. Death may be due to the original disease producing SE, medical complications or AED related toxicity. Age, etiology of SE and duration of seizures are important determinants of mortality and morbidity. Children have lower mortality rates than adults. Elderly patients generally have a poorer outcome. Encephalitis and cerebral hypoxia are associated with higher mortality compared to AED withdrawal or alcohol withdrawal SE. Duration of SE is also an important determinant of outcome. SE lasting less than 30 minutes carried a 2.7% mortality risk, compared to 19% for SE lasting less than 1 hour and 32% for SE lasting more than 1 hour.[25] Those patients who survive SE usually have high morbidity. Deterioration in functional outcome is present in 25% of patients with 10% requiring long-term care.[26] The outlook for patients with RSE is even more dismal with a mortality of nearly 40%. Only 20% return to baseline activities on discharge.[27]

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F. RAPIDLY PROGRESSIVE NEUROMUSCULAR DISORDERS WITH RESPIRATORY FAILURE

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INTRODUCTION

Broadly speaking, respiratory failure can be caused either by cardiopulmonary disease or a primary neurological disorder. The latter can be due to CNS affection as in cervical myelopathy or brainstem disturbance or due to neuromuscular diseases (NMDs) which affect the lower motor neuron (LMN). The motor unit or LMN comprises of the anterior horn cell, spinal root, peripheral nerve, neuromuscular junction (NMJ) and muscle. Specific NMDs have a predilection for one or more of the above sites of the motor unit. For instance, myasthenia gravis (MG) affects the NMJ, poliomyelitis damages the anterior horn cells, while polymyositis affects the muscles.

Respiratory failure and autonomic derangements are frequent accompaniments of NMD and can be fatal if not recognized and treated in time. Guillain-Barré syndrome (GBS) and MG are the most common rapidly progressive NMDs. Other less common but nevertheless important NMDs include inflammatory myopathies (polymyositis and dermatomyositis), organophosphate poisoning, porphyria, rhabdomyolysis, Lambert-Eaton syndrome and botulism. In the last few years, critical illness neuropathy and myopathy are being increasingly diagnosed in intensive care units where patients with nonneurological illnesses like burns and sepsis develop newly acquired weakness and an inability to be weaned off the ventilator. This chapter focuses on respiratory failure caused by rapidly progressive NMDs.

GENERAL CONSIDERATIONS IN SUSPECTED RESPIRATORY FAILURE

Impending respiratory failure must be recognized and managed promptly. Hypoxemia, hypercapnia and acidosis may not be apparent until respiratory failure is advanced. So action needs to be taken before they occur. Trying to intubate and resuscitate a gasping patient reflects poor clinical judgement. Warning signals of respiratory compromise include a weak cough with inability to clear secretions, rapid shallow breathing, air hunger with excessive use of accessory respiratory muscles, forehead sweating, tachycardia, disturbed fragmented sleep and orthopnea. Dysphagia is closely associated with respiratory distress and in the early stage, causes cough while swallowing and nasal regurgitation. Diaphragmatic weakness causes paradoxical breathing. Disorientation and irritability can be early features of hypoxia while hypercapnia may cause drowsiness. Sleep often precipitates respiratory distress in NMDs. Depressed activity of the accessory muscles during sleep worsens the hypoventilation already present. It is rare for respiratory muscle weakness to occur in isolation. Weakness of the neck, trunk and proximal limb muscles is usually present and must be looked for.

Measuring chest expansion during inspiration, asking the patient to cough and swallow liquids and the single breath count are simple bedside tests to evaluate the strength of the respiratory muscles. An individual with normal respiratory reserve can count loudly up to about 50 in a single breath after a deep inspiration. A single breath count of about 25 roughly corresponds to a forced vital capacity (FVC) of more than 2 liters.[1] Significant respiratory impairment is associated with a single breath count of less than 15.

Spirometry with assessment of respiratory muscle strength complements the clinical evaluation and provides valuable information. The FVC, negative inspiratory force (NIF) and positive expiratory force (PEF) are useful in assessing respiratory muscle function. It is possible to perform these tests by the bedside in the intensive care unit (ICU) with suitable equipment and qualified respiratory therapists. The FVC is normally about 60–70 mL/kg. If it falls to about 30 mL/kg, the cough becomes weak and the patient complains of dyspnea. An FVC of 15 mL/kg or 1 liter is an indication for mechanical ventilation. Tidal volume changes little in the early stage of ventilatory failure, but falls dramatically with advanced respiratory muscle weakness. The NIF is a measure of alveolar ventilation while the PEF tests the ability to cough and clear the airways. Forced vital capacity and NIF may give a false low reading if the facial and bulbar muscles are significantly weak or if there is an air leak around the mouthpiece during testing.

Patients with overt respiratory failure, shock, impaired consciousness or evidence of active aspiration are immediately intubated and ventilated. Others who have respiratory compromise but are otherwise stable should be closely monitored. When in doubt about whether to intubate or not, it is better to take the former course.

DIAGNOSIS OF THE UNDERLYING NEUROMUSCULAR DISEASES

A recent respiratory or gastrointestinal infection preceding the onset of symptoms provides the clue to a GBS or an exacerbation of MG. Acute gastrointestinal symptoms are also seen in botulism, while abdominal pain often precedes an attack of acute intermittent porphyria (AIP). Recurrent episodes of generalized weakness suggest hypokalemic periodic paralysis. Diurnal fluctuations of symptoms with increased fatigability point to the diagnosis of MG as do intermittent diplopia, difficulty in chewing, dysphagia and nasal regurgitation. A history of drug ingestion and insect bite (tick paralysis) should also be inquired into.

Neuromuscular diseases have a specific pattern of muscle weakness. Generalized areflexic weakness of all limbs is a feature of GBS. Predominant proximal muscle weakness with preserved deep tendon reflexes occurs in inflammatory muscle disease. Ptosis, eye closure weakness, bulbar involvement and proximal limb weakness with preserved reflexes point to MG. Fluctuations in pulse and BP with sweating and sphincter disturbance indicate an autonomic disturbance, commonly seen in GBS, porphyria and botulism. Skin rash is a typical feature of dermatomyositis.

Electromyography and nerve conduction study (EMG and NCV) is a valuable tool in the diagnosis of NMDs. It accurately localizes the anatomical site of involvement. Laboratory investigations are ordered depending on the probable diagnosis of the NMD. Acetylcholine and muscle-specific tyrosine kinase (MUSK) receptor antibodies are present in MG, while porphobilinogen in urine and delta-aminolevulinic acid in serum point to AIP. Serum creatine phosphokinase is significantly raised in inflammatory myopathies.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome is the most common cause of rapidly progressive neuromuscular weakness. It is an immune-mediated polyradiculoneuropathy with an annual incidence of 1–2/100,000.[2] In about two-thirds of patients, an antecedent gastrointestinal or upper respiratory tract infection is reported up to 3 weeks prior to the onset of symptoms. Campylobacter jejuni is the most frequent pathogen identified. It is associated with ganglioside 1 (GM1) antibody and results in a more severe, predominantly axonal disease.

Guillain-Barré syndrome manifests in different forms. Acute inflammatory demyelinating polyneuropathy (AIDP) is the most frequent type with predominant demyelination of the proximal roots and peripheral nerves. Acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN) are less common forms of GBS with predominant axonal degeneration. They are usually associated with a more severe form of disease and a poorer prognosis.[3] GBS usually presents acutely with paresthesiae in the feet and distal lower limb weakness which rapidly ascends over hours or days to involve the trunk and upper limbs. Severe diffuse back pain with or without radiation to lower limbs may be a presenting feature in some cases and can be mistaken for an acute lumbar disk prolapse. The limb weakness is usually symmetrical and involves the proximal and distal muscles. It progresses to reach a peak up to 4 weeks from onset, though most patients plateau within 2 weeks. Bifacial weakness occurs in nearly 70% of cases. Generalized areflexia is a salient feature in most cases. EMG or NCV studies reveal segmental demyelination in AIDP and also identify the axonal variety of GBS. CSF proteins are elevated after the first week of illness. Cells are very few or absent. Increased cells (>50 cells) should raise the possibility of another illness like human immunodeficiency virus (HIV), poliomyelitis, neurosarcoidosis, lymphoma or leukemia with peripheral nerve or root infiltration.

Bulbar and respiratory muscle weakness and dysautonomia are dreaded complications of GBS. Respiratory failure requiring ventilatory assistance occurs in about one-third of patients. Those with rapidly progressive weakness (<7 days from onset) and involvement of shoulder and neck muscles have a high likelihood of progressing to respiratory failure. An FVC less than 15 mL/kg (<1 liter) or NIF less than 20 cm of water or a $PaCO_2$ above 50 mm Hg usually require intubation and ventilation. A decline of more than 30% in the above parameters also warrants intubation, even though levels may not be too low. Patients with bulbar involvement, aspiration pneumonia and medical comorbidities like congestive heart failure may need ventilation earlier than others. Noninvasive positive pressure ventilation (NIPPV) is tried in some mild cases, but it is generally not recommended because of the risk of aspiration, and also because most patients will require ventilation for a prolonged period of time. Autonomic disturbances occur in most GBS patients. Sudden episodes of hypertension or hypotension, along with cardiac arrhythmias—tachyarrhythmias, severe bradycardia and even asystole—can be life-threatening. They are more likely to occur during tracheal suction and position change. Severe leg weakness in GBS can lead to deep venous thrombosis (DVT) and pulmonary embolism.

Plasma exchange (PE) or intravenous immunoglobulins (IVIg) are recommended in GBS with significant and progressive motor weakness. Treatment should be instituted as early as possible, usually within 7 days of onset. Both forms of therapy are equally effective in reducing the risk of developing respiratory failure and hastening recovery.[4] In PE, five cycles are usually given at alternate day intervals—about 40–50 mL/kg for a total of 200–250 mL/kg. Replacement fluid is usually albumin or saline. Hypotension and sepsis are significant adverse effects of PE. IVIg is easier to administer, but is more expensive. The recommended dose is 400 mg/kg per day for 5 days. Intravenous immunoglobulin is contraindicated in renal failure and may rarely cause myocardial and cerebral ischemia due to hyperviscosity.

Guillain-Barré syndrome carries a 3–10% mortality risk. Respiratory failure, cardiac arrhythmias and sepsis are the main causes of death. Although most patients eventually recover with minimal deficits, about 20–30% are left with significant disability.[3] A poorer outcome is associated with axonal variants, age over 60 years, bed-bound, intubated patients, rapid onset with maximum deficit within 7 days and prior diarrheal illness.[5]

MYASTHENIC CRISIS

Myasthenia gravis is an autoimmune disorder of the NMJ characterized by the presence of antibodies directed against the acetylcholine postsynaptic nicotinic receptors. The clinical hallmarks of MG are its fluctuating course with diurnal variation of symptoms and fatigable muscle weakness. The ocular, bulbar, neck and proximal limb muscles are most commonly affected. Myasthenic crisis (MC) is an acute

exacerbation of generalized MG with inability to swallow and respiratory muscle weakness requiring mechanical ventilation. About 15–20% of patients with generalized MG experience a crisis at some point in their illness, most often during the first year after onset of symptoms.[6]

Although MC can occur as a result of disease progression, it is often precipitated by certain aggravating factors. Intercurrent infections, especially aspiration pneumonia, are a common precipitating factor, responsible for about 40% of MC cases. Drugs known to aggravate myasthenic symptoms include antibiotics like aminoglycosides (gentamycin, tobramycin), fluoroquinolones (ciprofloxacin, levofloxacin) and macrolides (erythromycin), antiarrhythmics (procainamide and quinidine), quinine, curare and penicillamine. Pregnancy, surgery and stress can also precipitate a MC. Administration of high-dose steroids to newly diagnosed generalized MG patients can paradoxically worsen symptoms and precipitate a crisis. So, steroids should be started at a low dose and gradually escalated to the desired level.

Myasthenic crisis with respiratory failure and stridor may, at times, be the presenting feature of this illness.[7] A high index of suspicion is needed to diagnose MG in this situation of unexplained respiratory failure. MG is diagnosed by a positive edrophonium or prostigmine test, EMG evidence of significant decrement of muscle action potentials on repetitive electrical stimulation and presence of acetylcholine receptor or MUSK antibodies in the serum. In the edrophonium test, IV tensilon is given initially as a 2-mg test dose, followed 90 seconds later by 8 mg to a total of 10 mg. Onset of improvement usually occurs in 30 seconds and lasts 5–10 minutes. As this drug can cause severe bradycardia and other cholinergic side effects, it is best to administer it in the ICU. Intramuscular neostigmine (2 mg) can be used as an alternative to edrophonium. Maximum improvement with this drug usually occurs in 15–30 minutes. Acetylcholine receptor antibodies (AchR Ab) are detected in about 85% of generalized MG.[8] Antibodies to the MUSK are found in about 40% of those who test negative for AchR antibodies.[9] Muscle-specific tyrosine kinase MG commonly occurs in females of 20–30 years old without thymoma. They have prominent orofacial and respiratory muscle involvement at onset and are more likely to develop MC.[10] Ocular symptoms are usually absent. They respond poorly to cholinesterase inhibitors. A CT scan of chest is done to rule out a thymoma.

Early signs of respiratory distress must be closely looked for. Indications for mechanical ventilation have been mentioned earlier. An optimal ventilator setting is chosen to combat fatigue and promote lung expansion. This can be done by selecting assist control with positive end-expiratory pressure (PEEP) of 5 cm of water. To avoid lung injury, lower tidal volumes at 6 mL/kg and faster rate of 12–16 breaths/minute may be selected. Noninvasive ventilation with BIPAP (intermittent bilevel positive airway pressure) may be used to prevent atelectasis and avoid or delay intubation and mechanical ventilation in some patients with early MC. Hypercapnic patients are unlikely to benefit from BIPAP.[11] Patients with swallowing difficulty should have a nasogastric tube inserted for feeds and medications.

Both PE and IVIg are equally efficacious in MC. Therapeutic benefit occurs in about 5–7 days with either treatment. PE is the preferred treatment option in a recent literature review.[12] High-dose corticosteroids should be given once the patient is on mechanical ventilation in order to induce a remission. The recommended dose is 60–100 mg/day until improvement in symptoms is noted, after which the dose is gradually tapered. Excessive use of anticholinesterase drugs may occasionally cause respiratory distress with increased salivation, lacrimation, diarrhea and bradycardia. This is called a cholinergic crisis. When it is difficult to differentiate it from an MC, it is best to stop the drug. In any case, once the patient is on a ventilator, this drug is withheld as it tends to increase respiratory secretions. It is reintroduced once the patient recovers from the crisis and is taken off the ventilator.

CRITICAL ILLNESS NEUROPATHY AND MYOPATHY

They are common causes of new onset weakness in critically ill patients who have been admitted to the ICU for some other reason. They are suspected when patients are unable to be weaned off the ventilator in the absence of any sedation. Critical illness myopathy (CIM) is more frequent than critical illness neuropathy (CIN), but they often coexist.[13] Long-term use of high-dose steroids is more likely to cause CIM, while CIN occurs in about 70% of patients with sepsis and multiorgan failure. Other predisposing factors include hyperglycemia, inotropic support, use of neuroparalytic agents and long ICU stay with prolonged ventilation.

Motor weakness in these patients ranges from moderate paresis to complete areflexic quadriplegia. Muscle wasting and hypotonia also occur. Facial weakness and ophthalmoparesis are not seen, so, if present, other conditions like MG or GBS must be excluded. A glove and stocking sensory impairment occurs in critical illness polyneuropathy (CIP). CPK may be normal or mildly elevated in CIM. EMG or NCV studies may be normal or show evidence of axonal neuropathy or myopathy.

There is no specific treatment available, but their occurrence can be reduced by minimizing the use of high-dose steroids and neuromuscular blocking drugs, adequate control of infections and effective blood sugar control. In patients who survive sepsis and multiorgan failure, muscle strength recovers slowly over months.

ORGANOPHOSPHATE POISONING

Organophosphates (OP) are used as insecticides and are available as household products. In India, they are frequently used for suicidal poisoning. They are potent cholinesterase inhibitors. They bind and inhibit red blood cell (RBC) acetylcholinesterase, which results in excess amounts of

acetylcholine stimulating muscarinic and later nicotinic receptors.[14] Symptoms of excess acetylcholine include pinpoint pupils, diarrhea, bradycardia, increased bronchial secretions, salivation and sweating. Widespread fasciculations are also observed. Weakness of proximal limb, bulbar and respiratory muscles appears 24–96 hours later, which may require mechanical ventilation. This stage mainly occurs with lipophilic OP due to nicotinic receptor-induced NMJ disturbance. Measurement of RBC acetylcholinesterase activity correlates with the degree of toxicity. Treatment consists of immediate gastric lavage through nasogastric tube, management of respiratory failure with 100% oxygen and mechanical ventilation and administration of large doses of IV atropine and pralidoxime (see Chapter Critical Care in Poisonings).

LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton Myasthenic Syndrome (LEMS) is an NMJ disorder caused by antibodies directed against voltage-gated calcium channels (VGCC) on presynaptic motor nerve terminals. They inhibit the entry of calcium into the nerve terminals which is required for acetylcholine release, resulting in the presence of fewer acetylcholine vesicles in the synapse. In about two-thirds of cases, LEMS occurs as a paraneoplastic disorder, usually secondary to small cell carcinoma of the lung. The neurological symptoms may precede the tumor. In the remaining one-third of cases, LEMS presents as an autoimmune disorder without underlying cancer. These nonparaneoplastic cases occur more frequently in females and younger patients and can occur with other autoimmune disorders.

Symmetrical proximal muscle weakness in lower limbs followed by upper limbs occurs. It is worse on initiating a movement, improves with physical activity, but fatigues with prolonged sustained effort. Unlike MG, ptosis, ophthalmoparesis and bulbar symptoms are rarely seen. Respiratory muscle involvement is also uncommon in LEMS, though occasional cases presenting with respiratory failure have been reported.[15] Deep tendon reflexes may be diminished or absent, but may be elicitable after mild muscle contraction. Autonomic symptoms (dry eyes, reduced saliva, constipation and decreased sweating) also occur in LEMS.

Lambert-Eaton Myasthenic Syndrome is diagnosed by the presence of VGCC antibodies in serum and characteristic EMG changes of reduced compound muscle action potential (CMAP) amplitude and incrementing response on repetitive high-frequency stimulation. LEMS patients must be thoroughly searched for a malignancy. Treatment of the underlying cancer, if present, improves muscle strength. Acetylcholinesterase inhibitors (pyridostigmine) also improve symptoms, but not as effectively as in MG. 3–4, diamino pyridine blocks voltage-dependent potassium conductance, thereby facilitating acetylcholine release. Corticosteroids, PE and IVIg have also shown some benefit.

ACUTE INTERMITTENT PORPHYRIA

Acute intermittent porphyria is an autosomal dominant disorder characterized by recurrent attacks of acute motor neuropathy resembling GBS.[16] It is caused by deficiency of porphobilinogen deaminase enzyme. An attack of porphyria is often precipitated by drugs like sulfonamides, steroids, phenobarbitone and phenytoin as also in pregnancy, fasting and alcohol. The porphyric crisis typically begins with acute abdominal pain mimicking a surgical abdomen. Soon thereafter, CNS and psychiatric disturbances in the form of confusion, agitation, hallucinations and seizures occur. Within 48–72 hours, a severe symmetric, rapidly ascending predominantly motor axonal neuropathy resembling GBS develops. Proximal upper limb muscles can be maximally affected. Cranial nerves and respiratory muscles are also involved. Autonomic disturbance due to sympathetic overactivity causes pupillary dilatation, tachycardia and hypertension. The urine turns brown, if allowed to stand, due to the formation of porphobilin. Elevated levels of urinary porphobilinogen and delta aminolevulinic acid are seen. AIP is treated with IV glucose and hematin (4 mg/kg daily for 4 days).

POLYMYOSITIS AND DERMATOMYOSITIS

These inflammatory myopathies are characterized by muscle weakness, elevated blood creatine kinase (CK) levels and inflammatory changes on muscle biopsy. Dermatomyositis (DM) is more common than polymyositis (PM) and occurs mainly in children, whereas PM is usually seen in adults. They are associated with other autoimmune connective tissue disorders like systemic lupus erythematosis, scleroderma and rheumatoid arthritis and also carry an increased risk of malignancy. DM and PM present with acute or insidious onset of proximal greater than distal limb weakness. Ocular motor weakness does not occur. The main difference between the two disorders is a characteristic skin rash seen in DM which usually accompanies or precedes the muscle weakness. Bulbar and respiratory muscle involvement are uncommon but can rarely be the predominant symptom.[17] Orticosteroids are the mainstay of treatment. Other immunosuppressive drugs like methotrexate, azathioprine or mycophenolate mofetil are considered in those who do not respond to an adequate trial of steroids. IVIg is effective in improving muscle strength and resolving the immunopathology of DM and possibly PM.[18] Plasma exchange has not shown any benefit in these disorders.

RHABDOMYOLYSIS

Rhabdomyolysis refers to an acute, severe necrosis of muscle fibers with release of cellular components into the blood and urine. Myoglobinuria is the resultant excess amount of myoglobin in the urine, which imparts a dark-brown color to it. Some important conditions causing rhabdomyolysis include

inflammatory myopathies (viral myositis, pyomyositis), traumatic crush injuries, snake venom, neuroleptic malignant syndrome and overdose of cocaine, heroin and alcohol. Rhabdomyolysis presents with acute generalized pain, swelling, tenderness and weakness of muscles. Proximal limb girdle muscles are more severely affected than distal muscles. In fulminant cases, respiratory muscle involvement leads to respiratory failure. Rhabdomyolysis is associated with markedly elevated CK levels (in thousands) and myoglobinuria, with oliguria/anuria and acute renal failure.[19] Hyperkalemia secondary to muscle breakdown and renal insufficiency also occurs. The mainstay of treatment is aggressive hydration to prevent renal failure. Intermittent hemodialysis is indicated for resistant hyperkalemia, oliguria/anuria, volume overload or metabolic acidosis.

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G. PERIOPERATIVE NEUROLOGICAL CARE

Late Sohrab K Bhabha

GENERAL CONSIDERATIONS

The demands of contemporary neurosurgery on critical care resources can be considerable. A good working rapport between intensivist, neuroanesthesiologist, neurologist and neurosurgeon does much to facilitate and simplify critical care. The practice of the neurologist or neurosurgeon *alone* assuming charge of critical care, while sometimes unavoidable, is to be strongly discouraged. Experience indicates that the *intensivist* should be the team leader during this crucial phase. It is also appropriate that the intensivist be involved in the preoperative care of the person whom she or he will continue to manage through critical perioperative and postoperative phases. It need hardly be stated that the results of painstaking neurosurgery can all too easily be undone, in more than one sense, by unskilled postoperative management. The scope of this chapter is to outline the critical care of the neurosurgical candidate.

PREOPERATIVE CARE

Intracranial Hypertension

The management of intracranial hypertension (ICH) in a variety of settings is discussed elsewhere. In the present setting, tumors and intracranial hemorrhage are possibly the most common causes of ICH. As always, the structural and functional bases for ICH require consideration. The operative mechanism of ICH may then be best addressed. If an intracranial drain is in position, extreme caution must be exercised in venting pressure, since intracranial compartmental shifts may pre-exist and any acute change may be disastrous. Corticosteroids are usually effective in the management of persons with peritumoral edema. Dexamethasone (16–32 mg/day), or an alternative steroid, may be started as soon as the diagnosis is made (*excepting* in suspected cerebral lymphomas) and preferably at least 48 hours prior to surgery. If the response is poor, the daily dose maybe elevated to 100 mg/day. For acutely decompensating situations, for example, impending herniation, a bolus of 100 mg may be followed by a similar daily maintenance dose. This measure, sometimes combined with an intravenous mannitol bolus (at times preceded by furosemide), hyperventilation, or both, will salvage most situations.

Seizures

Seizures, generalized or partial, are most often tumor- or bleed-associated phenomena in this setting. The incidence of seizures is higher in primary brain tumors than in secondary ones, with the exception of metastatic melanoma, which is frequently associated with seizures. Uncontrolled seizures lead to aggravation of an already decompensated intracranial pressure balance. Seizures may be anticipated in several supratentorial epileptogenic conditions, when prophylactic anticonvulsant drug (ACD) therapy should be considered. The evidence base for such prophylactic ACD use is slim.[1,2] It must also be added that contemporary literature seems to point to the underlying pathology, rather than the procedure, as the provocative factor. The presence of a seizure-provoking lesion should not prevent a search for coexistent metabolic derangements which lower seizure threshold, such as hypocalcemia, hyponatremia, hypoglycemia, alcohol-withdrawal and hepatorenal compromise. Patients with primary or secondary brain tumors who receive iodinated radiologic contrast media are at an increased risk for seizures; pretreatment with 5–10 mg oral dose of diazepam, 1 hour prior to contrast injection, reduces the incidence of such seizures.[3]

For most purposes, phenytoin is a satisfactory acute-care ACD which is available in several dosage forms. In previously untreated persons, a loading dose *must* be administered orally (15–18 mg/kg over 24 hours) *or* intravenously (rate not exceeding 50 mg/minute), preferably while monitoring heart rate and BP. We prefer oral loading. Subsequently, a daily dose of 5 mg/kg will usually maintain therapeutic serum levels. Stable serum levels should be ensured *preoperatively,* as far as possible. A seizure on the operating table is an uncommon but dreaded event. Newer agents like levetiracetam, lamotrigine, topiramate and lacosamide are alternatives to phenytoin, if the latter is contraindicated or produces side effects. Levetiracetam is, at times, preferred to phenytoin due to its better safety profile. It can be administered intravenously as well, if required. The duration of continued prophylactic ACD use is contentious; current literature appears to indicate that their use must be based upon the epileptogenic potential of underlying pathology. The presence of preoperative epilepsy or seizures requires altogether different considerations.

PERIOPERATIVE CRITICAL CARE

Head-Position and Airway

Appropriate head-positioning and fixation are vital steps, especially in the present era of microneurosurgery, image-guided techniques and neuronavigation, when head-position must be maintained over long periods of time. It is nonetheless important to ensure that the endotracheal tube is not compromised. Neck veins should not be obstructed in any way, since this will have an adverse effect on cranial venous return, hemostasis, brain edema and operating time.

Air Embolism

Twenty-five percent or more of persons operated in the sitting position may suffer from air embolism. This occurs as a result of air entry through torn cortical or diploic veins or dural

venous sinuses. Major air embolism causes right heart failure with catastrophic hypotension. Screening for a patent foramen ovale is preoperatively mandatory for any neurosurgical procedure in the sitting or "beach chair" position as well as in those procedures where one is likely to encounter prominent venous channels. Preoperative contrast-enhanced transcranial Doppler ultrasonography[4] and monitoring with transesophageal echocardiography as well as end-tidal PCO_2[5] help to define the presence of a patent foramen ovale and establish significant air embolism. Aspiration of air from a right atrial or Swan-Ganz catheter is both diagnostic and therapeutic. Inspired gas should be switched to 100% oxygen to decrease the volume-expanding effect of nitrous oxide on the air embolus, and the person should be turned to the left lateral recumbent position. Vasopressors may be required to support arterial pressure. Air embolism can lead to acute pulmonary edema,[6] pulmonary infarction, and also to delayed gas-embolic stroke.

Reversal

The abrupt elevation of intrathoracic pressure commonly associated with *rapid reversal* and its transmitted effects on intracranial venous pressure prompts many neurosurgeons to desist from this method of reversal. Their prime concerns are early intracranial bleeding and intracranial pressure elevation. Therefore, such teams continue to ventilate persons postoperatively and permit them to *emerge* or *float* out of the effects of anesthesia. If such a method is employed, it is *imperative* that the person be advised so preoperatively, to allay his anxiety when he awakens. *This cannot be overemphasized.*

Prophylaxis for *gastrointestinal bleeding, deep venous thrombosis* and *pulmonary* embolism are also important aspects of perioperative neurosurgical care and are considered elsewhere.

POSTOPERATIVE CRITICAL CARE

Effects of Anesthesia versus Immediate Neurologic Deterioration

Neurologically normal persons exhibit a variety of pyramidal signs as they emerge from general anesthesia and up to an hour (or two) thereafter. These include hyper-reflexia, ankle clonus and extensor plantar responses.[7,8] Similarly, a degree of confusion, mild worsening of previous hemiparesis, mild dysarthria and asterixis may all be residual anesthetic effects. In addition, patients undergoing craniotomy for large intracranial mass lesions awaken more slowly than patients after spinal surgery or craniotomy for small brain tumors.[9]

When confusion was not preoperatively present, its presence in the postoperative phase must be viewed as representing a fresh brain event; brain swelling or an evolving intracranial hematoma should be considered. Other worrisome pointers are progressive headache, vomiting, drowsiness, evolving hemiparesis or pupillary changes and *de novo* bradycardia. Any progressive or fluctuating deterioration should be presumed to be of serious import. Additive anesthetic and anticonvulsant toxicity may lead to toxic effects. Perioperative phenytoin administration has been associated with postoperative hiccups and vomiting. Persistent ophthalmoplegia (beyond a few hours) may indicate fresh brainstem vascular insult or may unmask a rare case of myasthenia gravis. Brain imaging with CT or MRI is the mainstay of structural redefinition in such circumstances and ought to be used early and as often as may be required. EEG and evoked response studies have a more limited role. At times, a substantial, transient change in postoperative neurological status may be anticipated, such as may occur in bulbar or ventilatory functions following some surgical procedures involving the brainstem, skull-base or craniovertebral region. This may necessitate anticipatory nutritional management (usually nasogastric intubation) or elective tracheostomy and short-term ventilation.

Hematomas

Hematomas can occur at the site of surgery, or remotely, in established spaces such as the extradural or subdural space. Occasionally, they are seen distant to the operative site. Established systemic hypertension predisposes a person to this complication; tumor (typically meningioma) and arteriovenous malformation resection are the most common settings. With gliomas, gross total resection is associated with a lower incidence of intraparenchymal hematoma development than subtotal resection.[10] Extradural hematomas can sometimes be prevented by tenting sutures, especially where the dura has been drawn away from the inner table. Subdural hematomas may result from abrupt brain decompression, such as occasionally occurs when spinal or ventricular drainage is established or when brain swelling responds to bolus mannitol. Surgery in the seated position also predisposes to subdural hematoma, because of traction on bridging veins, particularly after posterior fossa surgery.

Blood Pressure Control

Established *systemic hypertension* should be kept well-controlled both before and after craniotomy, since it has been associated with increased mortality in the critical care setting. The precise levels that represent a risk for cerebral edema postoperatively are difficult to define and depend on the surgical pathology, surgical trauma and preoperative control. In such persons, their regular antihypertensive treatment is started at approximately half to two-thirds the dose, as soon as possible postoperatively. Sedation often reduces antihypertensive requirements.

Hypertension after *carotid endarterectomy, angioplasty* and *arteriovenous malformation* surgery presents special problems. Malignant cerebral edema and hemorrhage may occur. *Dysautoregulated hyperperfusion* is thought to underlie such developments. When mean arterial pressure exceeds 110–120 mm Hg, nitroprusside or labetalol may

be the best choices to employ (see Chapter Hypertensive Emergencies and Aortic Dissection in the ICU). Nitroglycerin and nifedipine are preferably avoided.

Aneurysmal subarachnoid hemorrhage poses several challenges to the intensivist. Among these are the management of *vasospasm* and *dysnatremia*. The former may occur as early as a few days (2–4 days) of bleed or may set in as late as 2 weeks post-bleed. The result is variable ischemic brain insult, even catastrophic infarction, which may significantly mar the quality of outcome. The currently favored form of therapy is early intervention (either clipping via craniotomy or endovascular interventional obliteration) followed by a combination of induced hypertension, intentional hypervolemia and hemodilution, also known as "triple H therapy".[11] This form of therapy has never been subjected to controlled study, however.[12] Sodium metabolic derangements related to subarachnoid hemorrhage are a complex of disorders, as yet not fully pathophysiologically understood. Generally, hypernatremia carries a graver prognosis than hyponatremia does.[13] Bedside cerebral microdialysis is establishing itself as a useful tool for directly monitoring regional cerebral metabolic changes, some of which may help us to define impending neurological events.[14]

Intracranial Hypertension

Intracranial hypertension may be heralded by a failure to awaken as expected in the immediate postoperative period, a delayed change in the level of arousal (consciousness) after initial recovery, or the development of an unexpected change or loss of neurological function. Its important causes include hematomas (discussed earlier), perilesional brain edema, hydrocephalus, tension pneumocephalus and brain infarction (discussed later). Neuroimaging usually differentiates these and guides more specific treatment.

Postoperative *perilesional brain edema* peaks at 36–72 hours. The tempo of evolving ICH is slower in edema than in hematomas. Patients usually awaken as expected from anesthesia, but between 6 and 36 hours postoperatively, they become lethargic or develop fresh neurologic deficits. Brain imaging is obtained to exclude a bleed; as soon as this is done, the steroid dose is increased and free water administration is decreased. Further measures to monitor and combat the resultant raised intracranial pressure, such as sedation and hyperventilation (discussed elsewhere), may be required.

Postoperative *hydrocephalus* is most often associated with posterior fossa or intraventricular neurosurgery, the latter carrying the greatest likelihood of introducing blood into the CSF pathways. Patients with symptomatic third ventricular tumors may abruptly develop hydrocephalus and decompensate to coma and sudden death. The latter phenomena are probably a result of *plateau waves*. A ventricular drainage procedure is most often indicated.

With the advent of skull base surgery, the incidence of *tension pneumocephalus* has increased. Continual efflux of CSF from the basal cisterns creates a negative pressure, which sucks in air intracranially. Operative measures to prevent this include dural closure, skull base reconstruction, re-expansion of the intracranial contents and the placement of an extradural drain. Clinical signs of tension pneumocephalus usually appear 2–4 days postoperatively, when the intracranial air, due to its mass effect, mimics a space occupying lesion. Persons at risk should be nursed in the head-low position, for 4 days postoperatively. A plain skull film or CT scan readily makes the diagnosis clear. Once diagnosed, 100% oxygen is administered and if rapid decompensation is encountered, needle aspiration or silastic catheter placement may be imperative. Water-seal drainage may be required to prevent reaccumulation. Definitive surgery may be the final corrective measure.

Postoperative Stroke

When encountered in the immediate postoperative setting, this event has invariably occurred intraoperatively. Precautions in this direction therefore must be adopted *before* and *at the time of surgery*. Rarely, brain infarction occurs as a postoperative event. Preventive measures include ensuring a normovolemic state and normal arterial pressure. The postoperative, volume-depleted, hypotensive, hyponatremic, altered hemorrhagic state predisposes to stroke. Careful fluid and electrolyte monitoring are therefore essential.

The goal of fluid and *electrolyte* management in the postoperative period is to keep the person normovolemic and normo to slightly hyper-osmolar, at the same time ensuring normal sodium balance. Several brain-related factors may cause fluid and electrolyte disturbances, e.g. secretion of antidiuretic hormone (SIADH) and cerebral natriuresis. These should be carefully considered and appropriately treated (see Section Fluid and Electrolyte Disturbances in the Critically Ill).

Fever and Infection

Unsustained fever below 38.5°C can usually be attributed to atelectasis and the postoperative state. Higher temperature or persistence beyond the first 6 hours requires further investigations. Clinical examination, chest X-ray, sputum and urine cultures are the next step. *Central fever* is distinctly uncommon and should only be diagnosed when unremitting hyperthermia (>40°C) occurs in patients with massive hemorrhage or basal brain lesions in proximity to the anterior hypothalamus. Fever may sometimes be due to a sinusitis, caused or exacerbated by nasogastric intubation over several days. Drug fever, usually associated with an antimicrobial or an anticonvulsant, must also be considered. When fever persists beyond 24 hours and is unexplained by the foregoing, spinal fluid must be examined. Bacterial meningitis must be differentiated from its aseptic counterpart.[15] This is not always easy, since glucose ratios and cell counts are not so helpful. Fever, CSF leak, peripheral leucocytosis and culture positivity are better differentiators and favor bacterial meningitis. *S. aureus* and Gram-negative bacilli are the leading causes of

postoperative bacterial meningitis. Even with satisfactory therapy, CSF cultures may still show Gram-negative bacilli for up to 2 weeks. CSF leaks require definitive management if treatment is to be lastingly effective. Other factors causing fever at this stage are craniotomy infections, subgaleal fluid collections or hematomas, salivary gland inflammation, deep venous thrombosis and acute adrenal insufficiency.

The use of prophylactic antimicrobials in *clean* neurosurgical procedures, whether monitoring ones (ICP monitoring, drains, microdialysis) or formal surgery, is undergoing a process of continual review and rationalization.[16] The emerging trend is away from prophylactic use (particularly for monitoring ones) and increasingly toward extremely brief (single-dose, single-day, 3-day) use in formal ones.

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SECTION

16

Critical Care after Open Heart Surgery

- Critical Care after Open Heart Surgery

CHAPTER 62

Critical Care after Open Heart Surgery

GENERAL CONSIDERATIONS

Open heart surgery has made great strides in India. The number of centers for open heart surgery in the large metropolitan cities of the country is increasing year by year. In our center, 12–15 open heart surgeries are performed every week, and very often half the surgical intensive care unit (ICU) beds are engaged at any one time in the postoperative care of these patients. Coronary artery bypass grafting (CABG) is the most frequently performed open heart surgery, followed in order of frequency by valve replacements, and by repair of congenital defects in the heart. Even so, the overall number of patients subjected to CABG has fallen significantly. Advances in cardiology which include reperfusion therapy, angioplasty, stenting and use of drug eluting stents have lessened the need for a surgical approach, except in complicated problems or following failure of other modalities. The recently developed sirolimus-coated coronary stent has been associated with very good results. There is now no significant difference when comparing stents with CABG for left main disease with regard to mortality figures, or of the composite end-point of death, Q-wave infarction or cerebrovascular accident.[1]

The success of good surgical technique and good perioperative care can be easily ruined if critical care in the postoperative period is poor. In our unit, the mortality following CABG surgery is less than 1%. In fact, in patients with good preoperative left ventricular function, the mortality over the last several years has been nil. The surgeons are taking on more and more patients with poor left ventricular function (often with ejection fractions in the region of 15–20%. Many of these poor-risk patients have associated problems in the form of aneurysmal dilatation of a part of the wall of the left ventricle, and blocked coronary arteries which not only need to be bypassed, but also require an endarterectomy. Patients who have a very poor pump function and have to be taken up for CABG surgery or some other open heart surgery, are often given dopamine support (5–7 μg/kg per minute) as a preoperative measure for 1–2 days prior to surgery. In spite of the complexity of the surgical procedures, the mortality in what are really poor-risk cases is less than 2%.

The frequently observed adverse effects related to cardiopulmonary bypass (CPB) as also the increasing age of patients undergoing cardiac surgery has led to the development of less invasive techniques. These include minimally invasive direct coronary artery bypass (MIDCAB) and off pump coronary artery bypass (OPCAB).

Minimally invasive direct coronary artery bypass differs from conventional CABG in that instead of the conventional median sternotomy incision, access is obtained via a left or right thoracotomy, a parasternal incision or a partial sternotomy. The surgeons in our unit do not use this technique, but prefer to use the OPCAB which is performed on a beating heart without using CPB. The OPCAB technique is now used in many centers in India and the rest of the world with very good results. CPB is reserved for surgery on complicated coronary artery disease, for the surgical management of aneurysms of the aorta or ventricular wall, for valve replacement surgery and for surgery on congenital heart defects. Off-pump CABG surgery has been shown to decrease complications and shorten time for recovery. High-risk patients, unsuitable for CABG surgery using CPB, can now be successfully operated upon by this off-pump procedure. Though technically refined, CPB is still an abnormal state of perfusion. Anticoagulation, hypothermia, the absence of pulsatile perfusion and trauma

to the cellular elements of blood by exposure to air, tubings, filters and suction, are necessary but harmful features of this abnormal circulatory state. The effects of CPB are to an extent responsible for a number of management problems encountered during the postoperative phase. It is therefore necessary for the intensivist to be aware of the basic procedure and problems during CPB. This chapter however confines itself to management problems after patients undergoing cardiac surgery have been transferred to the ICU for post-operative critical care.

MONITORING ON TRANSFER TO THE ICU

Before transfer to the ICU, the practice in our unit is to intravenously inject 500,000 units of aprotinin postoperatively, and then 500,000 units in an infusion over the next 12 hours, so that postoperative bleeding is reduced. Some units prefer to use the drug preoperatively and, if for any reason the risk of bleeding is increased, the postoperative dose can be suitably raised as well, up to 500,000 units/hour till the bleeding stops.

Patients are continuously monitored on arrival to the ICU. The arterial blood pressure is monitored through an arterial line, the central venous pressure (CVP) through a central venous line, the urine output by an indwelling Foley's catheter, the echocardiogram (ECG) by a single lead ECG, and the oxygen saturation by a pulse oximeter. In addition, in selected instances, temporary epicardial atrial and ventricular pacing wires are left in situ for a few days, for the management of arrhythmias.

A Swan-Ganz catheter is often inserted to measure the pulmonary capillary wedge pressure, particularly in patients with poor pump function or in patients with complex problems. Contrary to published literature we have noticed neither an increase in mortality nor morbidity following its use. The Swan-Ganz is removed on the third or the fourth day or even earlier.

The mediastinum and the left pleural space have chest drains, and the drainage is measured every hour to determine if excessive bleeding is present. When both internal mammary arteries have been used as grafts, or if for any reason the right pleural space has been opened, a chest drain in the right pleural space becomes imperative as well. The rectal temperature, the heart rate and the respiratory rate are continuously monitored. The patient has an endotracheal tube in place, which is connected to a ventilator. The ventilator settings are noted—in particular, the respiratory rate, the tidal volume, the minute ventilation, and the peak and pause inflation pressures.

A 12 lead ECG and a chest X-ray are taken immediately on arrival to the ICU. Blood is also collected for complete blood count (CBC), packed cell volume (PCV), platelet count, serum electrolytes, urea, creatinine, glucose, arterial pH and blood gases. Relevant studies in relation to the blood chemistry, clotting parameters, and arterial pH and blood gas analysis are repeated as and when necessary.

IMMEDIATE POSTOPERATIVE MANAGEMENT

Immediate postoperative goals include restoration of normal body temperature, monitoring of hemodynamic and respiratory functions with prompt correction of any abnormalities or complications that may arise, restoring and maintaining fluid, electrolyte and acid-base balance, and replacing blood loss which is estimated both clinically and by noting the volume of drainage through chest tube drains. Intravenous (IV) infusions should maintain adequate filling pressures within the ventricular chambers. The rate and quantity of IV infusions depend on the circulatory state after surgery, the ongoing blood loss and the urine output.

In our unit, patients undergoing CABG are often transferred from the operating theater with an ongoing infusion of nitroglycerin at a rate of 5–10 μg/kg per minute, to increase vascular capacitance in the immediate postoperative period, and to counter coronary artery vasoconstriction. They occasionally are also on an infusion of dopamine (5–7 μg/kg per minute), for immediate postoperative inotropic support. These infusions are tapered and stopped after the first 24 hours if the circulatory state is satisfactory, and the immediate postoperative period is uneventful. Aspirin (300 mg) is administered 8 hours after surgery and continued once daily throughout the postoperative period. After discharge, the patient should continue 150 mg daily on an indefinite basis. Low molecular weight heparin is begun on the second or the third day after surgery and continued for 7 days. Both aspirin and heparin may need to be omitted in the presence of excessive postoperative bleeding.

The following features are worthy of note in the immediate postoperative period—

- Serum K^+ levels during the early postoperative phase can fluctuate markedly. Serum K^+ should be maintained between 3.5 and 4.5 mEq/L.
- Uncontrolled hyperglycemia is frequent in diabetics and needs carefully titrated administration of insulin so as to keep the blood sugar less than 150 mg/dL. In nondiabetics, blood sugar levels to start with may also be high—between 250 and 350 mg/dL. Carefully titrated actrapid insulin is given every 4–6 hours to maintain blood sugar levels less than 150 mg/dL. Insulin is generally not necessary in nondiabetics after 48–72 hours.
- Significant acid-base disturbances, e.g. metabolic acidosis or metabolic alkalosis may be present and need to be corrected.
- Shivering is common, as the early period after CPB is characterized by a fall in the core temperature. Shivering commonly occurs during this phase, as patients begin to re-warm after the effects of the anesthetic and muscle relaxant begin to wear off. Shivering interferes with effective mechanical ventilation, and causes an increase in the CO_2 production. It also increases oxygen consumption

and myocardial work, thereby making undue demands on a heart recovering from the effects of aortic cross-clamping and CPB. Minute ventilation should be appropriately increased to counter increased oxygen consumption and CO_2 production till such time as the patient's temperature slowly rises and remains stable. This may take 2–8 hours. Severe shivering, particularly when associated with hemodynamic instability, should be countered by the use of a muscle relaxant (pancuronium 2–4 mg intravenously). This controls the shivering and allows the patient to rewarm slowly.

- Bleeding is one of the commonest problems encountered in the early postoperative period. Bleeding may be due to several causes—heparin rebound, acquired qualitative platelet defects due to CPB or drugs, thrombocytopenia, clotting factor deficiencies, local or systemic fibrinolysis, and disseminated intravascular coagulopathy.[2] The activated clotting time, bleeding time (BT), prothrombin time (PT), partial thromboplastin time (PTT) and platelet counts are routinely estimated and repeated as necessary. A full coagulation profile is often asked for, but results are generally available only after the lapse of some precious hours. Therefore, initial management of bleeding is more often than not empiric. Since heparin rebound is fairly common, (the PTT will be raised), protamine (50–100 mg) is given in an attempt to effectively neutralize heparin. Fresh frozen plasma should be given to replace a possible deficiency in the clotting factors. The prothrombin time will be raised in these patients. Desmopressin may be given in an infusion over 10 minutes, in a dose of 0.3 µg/kg, to increase levels of von Willebrand's factor and to restore platelet function.[3] Thrombocytopenia (<80,000/mm^3) or a prolonged template BT is managed by adequate platelet infusions. If the serum fibrinogen level is less than 125 mg/dL, 8 U of cryoprecipitate are administered. If there is evidence of fibrinogenolysis with high levels of fibrin degradation products (FDP), epsilon aminocaproic acid may be given in a dose of 5–10 g intravenously in the first hour, followed by an infusion of 1 g/hour for 3–5 hours. Transfusions of red blood cells or whole blood should be guided by the rate of blood loss, the hematocrit and the existing hemoglobin values in blood. We prefer to maintain a hemoglobin concentration of between 10 g/dL and 11 g/dL.

The surgical decision to re-explore the chest for excessive bleeding through chest tube drains is dependent on the volume and rate of blood loss, and the basic coagulation status. If this status (platelet count, CT, BT, PT, PTT, fibrinogen levels) is satisfactory, or if an existing coagulopathy has been adequately corrected, exploration is considered if the blood loss exceeds 1,000 mL in the first 12 hours. Sudden increase in the blood loss to more than 300 mL/hour for 2 hours should prompt a possible re-exploration. Blood loss of 300 mL in the first hour, 250 mL in the second hour and 150 mL/hour subsequently has been correlated with surgically correctable bleeding.[4] Surgeons generally prefer to err on the safer side and risk a re-exploration, rather than await a possible hemodynamic collapse. Re-exploration may be rewarded by the presence of a discrete major source of bleeding which can be promptly controlled. Not uncommonly, a number of small bleeding points are present. Evacuation of a clot and cauterization of these points generally suffice to stop the bleeding. It is of critical importance to realize that a sudden cessation or sharp decrease in the chest tube drainage in a hemodynamically unstable patient may be due to excessive bleeding within the chest with clots blocking the drains. If bleeding persists but drainage ceases, tamponade can result. A chest X-ray in these patients shows a pleural opacity, and the presence of hypovolemic shock should clarify the diagnosis. Urgent re-exploration with evacuation of the clots, with special attention to the bleeding points within the chest, is mandatory.

When bleeding from the chest drains is uneventful and within the normal range, the drains are generally removed by the third or fourth postoperative day. By this time, chest tube drainage is generally less than 100 mL/day. Some surgeons prefer to remove drainage tube earlier, by the second day.

An infrequent but life-threatening reaction soon after cardiopulmonary surgery is a protamine reaction. Parillo describes three kinds of reactions.[5] The first is caused by rapid administration of protamine; this leads to hypotension due to release of histamine from mast cells. The second is an anaphylactic reaction resulting in hypotension, bronchospasm and vasodilatory shock. Anaphylaxis is more frequently observed in diabetics exposed to protamine insulin and in patients with a history of fish allergy. Also, patients who have undergone cardiac surgery in the past are at greater risk. The third kind of reaction is due to heparin-protamine complexes causing a release of thromboxane from the capillary bed. This results in acute pulmonary hypertension, right-sided heart failure and a low-output syndrome with hypotension. Treatment consists in the use of steroids, antihistamines, inotropes, vasopressors and volume infusions. We are fortunate in not encountering serious life-threatening protamine reactions, or perhaps we have missed them, attributing hypotension and low-output states to other common causes.

CARDIOVASCULAR COMPLICATIONS

With cross-clamping of the aorta during CPB, coronary blood flow ceases, and there is global myocardial ischemia. Myocardial preservation is optimized by the use of potassium-rich cold cardioplegia at 4°C, administered directly into the coronary arteries every 20–30 minutes. The shorter the cross-clamp time, the quicker the recovery of the myocardium after bypass. Cross-clamp time of 120 minutes or even more is well tolerated, particularly by patients with good preoperative left ventricular function. Even so, there is a significant degree of transient depression in myocardial function, which may last

from 6 to 12 hours. This depression is often more marked and longer lasting if the cross-clamp time is excessive, particularly in patients who have poor left ventricular function to start with.

The important cardiovascular complications are discussed below.

Low-Output Syndrome and Hypotension

This is one of the most frequently observed and important complications after open heart surgery. A persistent low cardiac output in the immediate postoperative period is associated with an increased frequency of multiple organ dysfunction, chiefly involving the renal, respiratory, hepatic and central nervous systems. It is clinically manifested by cold peripheries, low systolic arterial blood pressure (<90 mm Hg), decreased urine output (<30 mL/hour) and increasing acidosis. If hemodynamic measurements are made, these patients are noted to have a lowered cardiac index (often <2.2 L/minute) and a low mixed venous oxygen saturation.

There are two points worth noting in the recognition of low-output states—

1. Low-output states can occur with a systolic arterial blood pressure more than 90 mm Hg when a compensatory increase in peripheral vascular resistance helps to maintain arterial blood pressure.
2. It is important to distinguish hypotension caused by low-output states from hypotension due to vasodilatation.

Hypotension due to vasodilatation generally occurs in the first 24 hours after surgery. Vasodilatation results from decreased sympathetic tone leading to a reduced peripheral systemic vascular resistance (<1,000 dynes/sec/cm^5). It should be suspected when hypotension is associated with warm peripheries and a normal to low CVP. Inhibition of sympathetic tone may be due to anesthetic agents used during surgery, and to a marked increase in venous capacitance that occurs during the rewarming phase. Patients after CABG surgery are often shifted to the ICU with a nitroglycerine infusion to counter postoperative coronary vasoconstriction. The infusion may be too rapid, or the vessels may vasodilate due to marked sensitivity to the drug. At times, vasodilatation is aggravated if the patient is on continuous dobutamine support. In the above instance, nitroglycerine infusions must be slowed or stopped and dobutamine replaced by dopamine. If both dopamine and dobutamine are being used for inotropic support, infusion rate of the former is increased and that of the latter reduced. Volume loading these patients further helps in restoring a satisfactory circulation.

Vasodilatation in the immediate postoperative period can occasionally also result from an adverse protamine reaction. Hypotensive vasodilatory shock after cardiac surgery has been attributed in some patients to a relative deficiency of vasopressin.[6] Administration of arginine vasopressin corrects this form of hypotension.

Low-output states can be due to reduced preload, to poor myocardial contractility, to an increased afterload, to cardiac tamponade, cardiac arrhythmias, to metabolic derangements or to the adverse effects of antiarrhythmic drugs. Fulminating sepsis can also result in a low-output severely hypotensive shock (Box 1).

Box 1: Causes of a low-output syndrome and/or hypotension

1. Reduced preload—
   - Hypovolemia due to blood loss, fluid loss, excessive diuresis
2. Increased afterload—
   - Vasoconstriction from increased endogenous catecholamine secretion
     - Painful stimuli
     - Hypothermia
     - Pre-existing hypertension
   - Vasoconstriction from excessive exogenously administered catecholamines
3. Poor pump function—
   - Myocardial depression (impaired contractility)—
     - Perioperative infarction
     - Functional depression (<24 hours)
     - Myocardial ischemia
     - Inadequate myocardial preservation, intraoperatively
     - Pre-existing poor ejection fraction
     - Uncorrected mechanical lesions
     - Incomplete vascularization
     - Mechanical valve dysfunction
     - Undetected or uncorrected valvular stenosis or insufficiency
   - Metabolic complications—
     - Hypo- and hyperkalemia
     - Hypomagnesemia
     - Hypercalcemia
     - Hypoxia, acidosis
4. Arrhythmias and conduction defects
5. Antiarrhythmic drugs
6. Cardiac tamponade
7. Vasodilatation—
   - Due to anesthetic agents
   - Iatrogenic (e.g. nitroglycerine)
   - Poor sympathetic tone (e.g. diabetes, elderly)
   - Relative deficiency of vasopressin
   - Protamine reaction
   - Anaphylaxis to a drug
8. Fulminant septic shock

It is important to consider each of these factors if appropriate treatment is to be administered. More than one factor is often present in a given patient—

- *Reduced preload* The commonest cause of a low cardiac output and hypotension in the postoperative period is a reduced preload due to hypovolemia. Hypovolemia is due to excessive bleeding, loss of tissue fluids and/or excessive diuresis. Hypovolemia immediately after transfer to the ICU can be due to insufficient return of fluids during CPB. It can also occur from leaking capillaries, a feature of the post-pump syndrome. Cold peripheries, hypotension, tachycardia, a normal rectal temperature and a low CVP

(<5 cm H_2O) suggest hypovolemia. If a pulmonary artery catheter is in place, the pulmonary artery occlusion pressure (PAOP) and pulmonary artery diastolic pressure are low—often less than 10 mm Hg. Hypovolemia is corrected by infusion of colloids, crystalloids, and by the transfusion of packed red blood cells if there is increased blood loss. In addition to a volume load, the patient is often also put on inotropic support.

- *Poor pump function* Poor pump function may be due to left ventricular dysfunction and failure, or due to right ventricular dysfunction and failure, or may result from a global hypokinesia. When severe, pump dysfunction leads to cardiogenic shock. As mentioned earlier, poor pump function may not be related to an intrinsic abnormality within the myocardium but to metabolic disturbances, to arrhythmias, and to the effect of antiarrhythmic drugs. Impaired ventricular function after CABG surgery can be due to perioperative or postoperative myocardial infarction or severe ischemia, to inadequate revascularization at surgery, or the post-CPB reperfusion injury. Some degree of postoperative functional myocardial depression is at times observed, particularly after prolonged or difficult cardiac surgery. This generally lasts for not more than 24–36 hours. Myocardial edema, ischemia and even myocardial necrosis can result from inadequate myocardial preservation during surgery. After valve replacement surgery, pump dysfunction with a low-output syndrome can result from mechanical valve dysfunction. Severe left ventricular failure besides causing a low-output syndrome with hypotension also results in an increased pulmonary capillary wedge pressure and pulmonary edema. This is recognized clinically on a chest X-ray and by noting a progressive increase in the peak inflation pressures while on the ventilator without any change in the ventilator settings.

  Severe right ventricular failure and global hypokinesia are characterized by a poor forward flow and poor tissue perfusion, but not necessarily by increased left ventricular filling pressures (i.e. increased pulmonary capillary wedge pressures).

  The management of poor pump function is dealt with in a previous chapter, but is briefly recapitulated below for convenience.

- Ensure that the left ventricular filling pressure is maintained between 15 mm Hg and 20 mm Hg. Associated hypovolemia is thus countered by a volume load.
- If a low-output syndrome with hypotension is observed in the presence of high filling pressures, use inotropic support to an extent that ensures a satisfactory increase in the cardiac output and blood pressure. A continuous infusion of dopamine 5–20 μg/kg per minute helps to raise cardiac output and blood pressure. Dobutamine has little α-adrenergic activity but pronounced β_1 and β_2 adrenergic activity. It increases cardiac output by increasing cardiac contractility and rate and by its vasodilating effect. In patients with a low-cardiac output and a marked increase in systemic vascular resistance, dobutamine is preferred to dopamine. Dobutamine is given in an infusion at 5–20 μg/kg per minute. Dopamine and dobutamine can be given together but in separate infusions, the dosage of each being titrated to obtain an optimal circulatory effect. When dopamine and/or dobutamine are ineffective, an epinephrine infusion is used in a dose of 1–10 μg/minute. Epinephrine increases myocardial contractility and rate and in higher doses raises the blood pressure through its α-mediated vasoconstrictor effect on peripheral vessels. Norepinephrine which has both α- and β-adrenergic activity increases both myocardial contractility and blood pressure. It is given in an infusion at the rate of 4–10 μg/minute. Amrinone and milrinone are two inotropic drugs which increase cardiac output independent of adrenergic stimulation. Milrinone is an effective vasodilator as well, and should be tried in patients with low-cardiac output who are severely vasoconstricted. The drug is given in a loading dose of 50 μg/kg over 10 minutes, followed by an infusion of 0.375–0.75 μg/kg per minute.

  In difficult cases, two or more inotropes and vasopressors may prove necessary to increase cardiac output and blood pressure.

- Severe right ventricular failure can result in a markedly poor forward flow and a shock-like state. Though right atrial and CVPs are elevated, pulmonary capillary wedge pressures need not be high. Volume load and inotropic support as outlined earlier form the mainstay of management.
- Intravenous frusemide should be used in the presence of pulmonary edema.
- A low-cardiac output with hypotension can result from a marked increase in the systemic vascular resistance (afterload). An increase in the afterload could be due to excessive endogenously produced catecholamines resulting from unrelieved pain, hypothermia, non-pulsatile flow during CPB, or pre-existing hypertension. An increased afterload can also be caused by exogenously administered vasopressors.

  Factors contributing to an increased afterload should be corrected when possible. A titrated dose of IV nitroglycerine or IV nitroprusside also reduces afterload. The current trend is to avoid using nitroprusside except in patients with marked hypertension unresponsive to nitroglycerine and other anti-hypertensive drugs.

- Hypoxia, metabolic acidosis and electrolyte imbalance, notably in relation to K^+, Mg^{++}, Ca^{++} can aggravate or cause myocardial dysfunction. These factors should be recognized and corrected. Antiarrhythmic drugs are myocardial depressants and may well contribute to myocardial dysfunction.
- Shock-like syndromes after cardiac surgery may be due to rhythm disturbances and should be promptly rectified. These may be missed, as with supraventricular

tachycardias with A-V block, or in A-V dissociation with a fast atrial and ventricular rate. Loss of effective atrial contraction may tilt the balance against the patient.

- Bradycardia can lead to a low-cardiac index and hypotension. This is because the cardiac output is a product of the stroke volume and heart rate. IV atropine or atrial or atrioventricular (AV) pacing at 80–100/minute can restore a normal circulatory state.
- Cardiac tamponade is an important cause of a low output hypotensive syndrome.
- Myocardial assist devices become necessary for cardiac support if poor pump function persists after optimizing rate, rhythm, preload, myocardial contractility, afterload, and if factors such as metabolic disturbances, arrhythmias and drug reactions are non-existent or stand corrected. Intra-aortic balloon pump support reduces the afterload of the left ventricle and helps to relieve myocardial ischemia. Patients with very poor ejection fractions who undergo CABG surgery or those who suffer complications during surgery should best have a balloon pump inserted in the theater before transfer to the ICU. Ventricular assist devices are more effective in increasing cardiac output as compared to the aortic balloon pump but we have no experience with these devices.

In summary, though a volume load and the use of inotropes is the usual response to a low output state and/or hypotension, it is important to tailor therapy appropriate to the cause. Thus, for example, the steps detailed above would provide only temporary respite in a patient whose low-cardiac output is due to tamponade or to graft closure.

- *Septic shock* Hypotension with a shock-like state which to start with is associated with a normal or high cardiac output and a lowered systemic vascular resistance, characterizes septic shock. This condition has been dealt with at length in an earlier chapter. Sepsis may occur within the first 48 hours after surgery, or may occur later and interrupt an otherwise satisfactory progress. Sepsis may arise from a source in the operation theater, or may be related to gadgetry used for invasive monitoring and treatment. Occasionally, it results from a seeding into the blood from a source of infection within the body, e.g. from the urinary tract, the lungs, an infected anal fistula, or an infected pilonidal sinus. It should be a dictum to avoid cardiac surgery till such time as a pre-existing infection is appropriately treated. Patients running even a low-grade fever should not be taken for elective cardiac surgery till the cause of the fever is discovered and eradicated.

In critically ill, low-output hypotensive patients' management is significantly assisted by monitoring and measurement of circulatory hemodynamics through a Swan-Ganz catheter.

Cardiac Tamponade[7]

Hemodynamic instability in the postoperative period should promptly arouse suspicion of possible cardiac tamponade. Hypotension, a low CO, tachycardia with shock-like state and evidence of a rise in the right or left or both atrial pressures should lead to a prompt ECHO study to help confirm the diagnosis. Cardiac tamponade is usually caused by a leak at the site of right atrial cannulation; the resulting hematoma compresses the right atrium and superior vena cava, restricting inflow of blood into the right atrium. There is a progressive elevation of right atrial and CVP with a fall in cardiac output, tachycardia and hypotension. A rising right atrial pressure with an impaired filling of the right ventricle leads to a loss of the Y-descent in the right atrial pressure tracing. Equilibration of pressures in the right and left heart may not be observed when tamponade is due to a localized hematoma pressing upon the right atrium. Exploration to remove the hematoma is mandatory.

Cardiac tamponade due to pressure on both right and left ventricles can occur with mediastinal bleeding or from an extension of the right atrial hematoma over the front of the heart, or from a leak at the anastomotic site of a graft in CABG surgery. In addition to the clinical features of hypotension and raised CVP, there is invariably a widening of the mediastinal shadow. Cardiac tamponade should always be thought of when brisk bleeding and drainage through the chest tubes suddenly lessen or cease and the X-ray chest shows a widened mediastinum. Tamponade can well occur even in the presence of well-placed mediastinal drains. An increasing mediastinal shadow on chest X-ray, a diastolic collapse of the right atrium and right ventricle on echocardiography, coupled with the clinical findings stated above is diagnostic of cardiac tamponade. These patients would show equilibration of the right and left heart pressures on a hemodynamic study. A volume load and inotropic support should be given and the patient promptly taken up for surgery in order to remove clots and blood causing the tamponade.

Perioperative Myocardial Infarction

The recent Bypass Angioplasty Revascularization Investigation study revealed that the incidence of Q-wave infarction after bypass surgery was 4.6%.[8] Possible causes of infarction include incomplete revascularization, hemodynamic stress (in particular, hypotension and arrhythmias) during surgery, or during intubation, diffuse atherosclerotic disease of distal vessels, formation and extension of a clot in an endarterectomized coronary vessel, coronary artery spasm, embolism or thrombosis of native coronary vessels or bypass grafts.[9,10]

The diagnosis of perioperative myocardial infarction is based on the following—

- Appearance of new Q-waves after surgery. ST-T changes occurring alone without Q-waves are less specific.
- Creatine kinase-myocardial band (CK-MB) levels which are significantly or markedly elevated (>80 mg/dL).[11] A mild to moderate degree of rise in CK-MB is to be expected after cardiac surgery, without signifying a fresh infarction.
- Peak troponin I levels greater than 3.7 µg/L and troponin T levels greater than 3.4 µg/L.[12,13]

- The presence of a new regional wall abnormality on echocardiography. It is worth noting that the removal of the restraining effect of the pericardium consequent to surgery may lead to a false positive reading of a new regional wall motion abnormality in the high anterior septal area.

Small perioperative myocardial infarcts do well; larger infarcts have a high postoperative mortality which may be due to pump failure or due to uncontrolled ventricular arrhythmias. Patients, who are hemodynamically unstable or those with a large area of the myocardium in jeopardy, should be taken to the catheterization laboratory to determine if a graft is occluded. If so, the graft should be opened up through a balloon plasty.

Cardiac Arrhythmias[14]

Postoperative cardiac arrhythmias are common. They should be promptly recognized and treated. Hypokalemia, hyperkalemia, acidosis, bleeding, poor pump function, ongoing myocardial ischemia, or perioperative myocardial infarction can all trigger arrhythmias in these patients. These precipitating factors should be looked for and, if present, promptly corrected. Excessive use of inotropics for cardiovascular support is an often forgotten cause of malignant ventricular arrhythmias. Nebulization of large doses of salbutamol in patients with airways obstruction can enhance supraventricular and ventricular arrhythmogenic activity in the postoperative phase of open heart surgery. Arrhythmias are commoner and more persistent in patients who have had an aneurysmorrhaphy or an aneurysmectomy performed during CABG surgery.

Arrhythmias may be supraventricular or ventricular. Premature atrial contractions may be ignored except when they trigger repeated episodes of atrial fibrillation, or compromise circulation in patients who depend on a synchronized atrial contraction for a proper stroke volume. Cordarone should be used to suppress ectopic activity in these patients.

Paroxysmal atrial fibrillation is frequently observed, generally occurring 2–3 days after open heart surgery. It often reverts to sinus rhythm spontaneously. In a recent multicenter study of patients undergoing CABG surgery, the incidence of atrial fibrillation was noted to be 27%.[15] The most common risk factor for peri- and postoperative atrial fibrillation is advanced age. If atrial fibrillation with a fast ventricular rate persists and compromises circulation, then the ventricular rate should be slowed. 300 mg of IV amiodarone is administered as a bolus, followed by an IV infusion of 700 mg–1 g of amiodarone over 24 hours. Conversion to sinus rhythm is frequently observed. The dose of amiodarone is gradually reduced over the next 2 days, oral amiodarone being finally substituted for the infusion as prophylaxis. IV digoxin, followed, if necessary, by 5 mg increment doses of verapamil can also be administered to slow the ventricular rate in atrial fibrillation (see Chapter Tachyarrhythmias in the Intensive Care Unit). Electrical cardioversion is unnecessary in most patients. It should only be used in the presence of acute decompensation caused by a very rapid ventricular rate, which is uncontrolled by IV digoxin. Repeated episodes of paroxysmal atrial fibrillation or persistent atrial fibrillation in the postoperative phase may be due to pericarditis or pulmonary emboli. IV dexamethasone 4–8 mg offers dramatic relief and a return to sinus rhythm when the underlying cause is pericarditis. Supraventricular arrhythmias are perhaps more frequent in patients who have had an endarterectomy of the right coronary artery during CABG.

Transient second and third degree AV blocks are common after valve surgery. These are best treated with the aid of atrial and ventricular epicardial pacing wires placed during surgery. AV sequential pacing at a rate of 80–100/minute is preferred because of the contribution of atrial systole to cardiac output.

Ventricular arrhythmias are life-threatening. Ventricular tachycardia, not responding to a bolus dose of lidocaine, and which results in hemodynamic instability, should be converted to sinus rhythm by a synchronized DC shock of 200 J. Ventricular fibrillation needs prompt cardioversion. If 200 J is unsuccessful, a 300 J DC shock should be used. A bolus dose of lidocaine (1–2 mg/kg) is given after cardioversion in ventricular fibrillation; this is followed by a maintenance lidocaine drip at the rate of 1–3 mg/minute. Frequent ventricular ectopy is also treated with lidocaine as detailed above. If this drug fails to control multiple ventricular ectopics, or the patient has recurrent ventricular tachycardia or fibrillation, amiodarone 300 mg intravenously is given as a bolus dose followed by 1 g in an infusion over 24 hours. This is continued for 2–3 days, and followed by oral amiodarone. Currently, amiodarone is used in preference to lidocaine and is the drug of choice in the treatment of ventricular tachycardia (see Chapter Tachyarrhythmias in the Intensive Care Unit). The use of beta-blockers (metoprolol) administered intravenously in a titrated dose often restores sinus rhythm in ventricular tachycardia unresponsive to lidocaine or amiodarone. Rarely overdrive pacing may be required for control of persistent or recurrent ventricular tachycardia.

In patients who have received digitalis, digitalis toxicity should always be considered in the presence of multiple ventricular ectopics, atrial tachycardia with block, AV dissociation and ventricular tachycardia. Digitalis toxicity can occur even with serum digoxin levels within the therapeutic range. Details of management of various cardiac arrhythmias have been dealt with in an earlier chapter (see Chapter Tachyarrhythmias in the Intensive Care Unit).

Pericarditis

Pericarditis is common in the first 3–7 days following CPB. A pericardial friction rub is always present, and may persist for over 5–7 days. In the asymptomatic patient, no treatment is required. Symptoms of the post-pericardiotomy syndrome generally occur 2–8 weeks after open heart surgery. Symptoms include fever, tachycardia, chest pain, a raised erythrocyte

sedimentation rate (ESR) (often close to 100 mm/hour), a left-sided pleural effusion, occasionally a pericardial rub, and a tendency to supraventricular arrhythmias. The clinical condition improves with the use of nonsteroidal anti-inflammatory agents, particularly indomethacin. If the condition still persists, we prefer a short course of corticosteroids; a small maintenance dose may be required for weeks or months. Rarely constrictive pericarditis is a sequel to the post-pericardiotomy syndrome.

Postoperative Hypertension

The incidence of postoperative hypertension with a systolic blood pressure more than 140–150 mm Hg occurs in over 40% of patients.[16]

The mechanisms of postoperative hypertension include: (1) elevated circulating catecholamine levels with excessive sympathetic nervous system activity; (2) rebound effect from withdrawal of preoperatively given beta-blockers; (3) pressor reflexes originating from the heart, coronary vessels and the aorta. Postoperative hypertension should be controlled promptly. Increase in systemic arterial blood pressure, which is most often seen in the immediate postoperative period, can cause an increase in postoperative bleeding, disruption of suture lines of the grafts, aortic dissection, increase in afterload with ventricular dysfunction, and an increased incidence of strokes. A mild to moderate rise in blood pressure is best treated with a titrated dose of nitroglycerin in an IV infusion. A sharp marked rise in blood pressure is treated with a titrated IV infusion of labetalol or sodium nitroprusside. Hypertension and tachycardia following beta-blocker withdrawal is treated with IV esmolol 50–250 µg/kg per minute or IV metaprolol. The need for oral antihypertensives after the first 2 days should be assessed for each patient. Oral beta-blockers should be restarted in patients who were on these drugs prior to surgery. They effectively control the hypertension and tachycardia in these patients.

RESPIRATORY CARE

Patients are generally weaned off ventilator support within 4–12 hours. Low risk, younger patients undergoing CABG surgery are often extubated in the recovery room before being transferred to the ICU. The indications for weaning are the same as those discussed in the Chapter Mechanical Ventilation in the Critically Ill. The patient must be awake, hemodynamically stable with no significant abnormality on an X-ray chest. He should not be tachypneic on disconnecting the ventilator, and the blood gases after being kept on a T-tube for 2 hours should show neither hypoxia nor hypercapnia. He could then be extubated. Pain relief is important to enable the patient to breathe freely. He should be given oxygen through nasal prongs so as to keep the O_2 saturation well over 90%. We have always weaned patients by the T-tube method and have never found the need to use synchronized intermittent mandatory ventilation (SIMV). In patients who are difficult to wean because of atelectasis or edema, we use continuous positive airway pressure (CPAP) before graduating to the T-tube, CPAP or biphasic positive airway pressure (BiPAP) through an orofacial mask can be continued after extubation. Patients with poor left ventricular function [left ventricular ejection fraction (LVEF) <20%)] those with respiratory complications, or serious complications involving other organ systems, are kept on ventilator support for 24–48 hours, or even longer. It is unwise to remove support prematurely in these patients. The increased work of breathing in hemodynamically unstable patients can induce respiratory fatigue, hypoventilation and atelectasis with a progressive deterioration in the cardiorespiratory system.

More prolonged ventilator support is often necessary in those with chronic lung disease, particularly those patients with airways obstruction. If case selection has been correct, these patients generally can be weaned off support within 12–48 hours. Nebulization with salbutamol 4–6 hourly and ipratropium bromide 12 hourly is of help in keeping the airways open. A marked difference between the peak and pause inflation pressures is a guide to the severity of airways resistance. Corticosteroids should be avoided except in patients who are steroid-dependent, or in patients with asthma, who have a severe exacerbation of airways obstruction after surgery. The arrhythmogenic effects of beta-2 agonists and aminophylline in these patients should be borne in mind. The dangers of wound sepsis, other infections, and poor healing always accompany the use of corticosteroids.

Factors predisposing to prolonged ventilator support with difficulties in weaning are listed in Box 2.

Box 2: Factors predisposing to prolonged ventilator support with difficulties in weaning following open heart surgery

- Stormy postoperative period
- Re-exploration
- Left ventricular (LV) dysfunction
- Renal failure
- Infection (sepsis, pneumonia)
- Malnutrition
- Chronic airways obstruction
- Injury to phrenic nerve
- Aged, debilitated, poor-risk patients
- Multiple organ dysfunction/failure
- Stroke/encephalopathy

PULMONARY COMPLICATIONS

These include pulmonary edema, acute respiratory distress syndrome (ARDS), atelectasis and nosocomial pneumonia.

- Pulmonary edema is generally due to raised left ventricular filling pressures consequent to left ventricular failure. Acute lung injury (ARDS) can occasionally result as a consequence of CPB even in the absence of infection or transfusion reactions. It is due to exposure of blood to foreign surfaces during prolonged CPB. Damage to the

alveolar capillary membrane is induced by clumping of platelets, leucocyte sequestration and activation of the coagulation cascade, the complement and the fibrinolytic system. The mortality against the background of recent cardiac surgery is over 70%.[17] Risk factors include hypertension, smoking, emergency surgery and a low-output syndrome after surgery.[18]

- Pulmonary atelectasis invariably occurs because of poor respiratory care leading to retained respiratory secretions. Good physiotherapy, proper suction and frequent change of posture are necessary, particularly in obese patients with short, thick chests. The use of positive end-expiratory pressure (PEEP) during ventilator support is of help in opening up atelectatic areas.

  The commonest cause of perioperative respiratory failure (Type III failure) is atelectasis. Atelectasis may present with obvious atelectatic shadows in one or both lung fields. It, however, often presents with small volume lungs on an X-ray chest with high diaphragms. The small lung volumes on either side need not be symmetrically equal. Clinically, the patient is tachypneic off the ventilator, breathes poorly, coughs poorly and ineffectively. This problem in our experience is commoner in females, particularly those with short, stocky chests. Ventilator support for a longer period with the use of PEEP helps to keep the lungs open. Physiotherapy and pain relief help in breathing and clearing secretions. After extubation these patients should be given either CPAP or BiPAP through the night and for several hours during the day to keep the lung volumes from shrinking.
- Nosocomial pneumonias are infrequent in our set-up. Remarkably enough, the incidence is higher in those with poor left ventricular function (see Section Fever and Acute Infections in a Critical Care Setting).
- Pleural effusion is common after cardiac surgery; it generally resolves spontaneously and should be tapped only if it produces symptoms. Rarely pleural effusion of moderate severity persists for weeks or months after CABG surgery. Infection, in particular tuberculosis, should be excluded. When noninfective and persistent, a pleurodesis generally solves the issue.
- *Diaphragmatic paralysis* Partial paralysis is frequent on the left side and is due to phrenic nerve injury or due to freezing of the phrenic nerve because of the ice slush used for myocardial preservation. The raised left dome of the diaphragm is generally not associated with increased morbidity. In a very small number of these patients, total one-sided diaphragmatic palsy may be symptomatic, in that it can cause left lower lobe atelectasis and pose problems in weaning from ventilator support. A paradoxical movement of the dome of the diaphragm on sniffing confirms diaphragmatic paralysis. Ventilator support may be required for a longer period of time in these patients. Bilateral phrenic nerve injury with diaphragmatic palsy occurs even more rarely. The patient becomes cyanosed on lying down and is promptly relieved on sitting up. We have had three patients with bilateral diaphragmatic paralysis following open heart surgery. Recovery occurred over a period of 6–10 weeks, during which time mechanical ventilator support was necessary.

If ventilator support is necessary for more than 14 days, an elective tracheostomy becomes necessary. The danger of sternal wound infection following a tracheostomy always exists, and this could involve the mediastinum to produce mediastinitis, mediastinal abscess, empyema, and a communication between the empyema and the mediastinal abscess. These complications are fraught with great danger and result in a very high morbidity and mortality. It is therefore unwise to do a tracheostomy when the sternal wound shows signs of infection. As far as possible, the operative wound must be clean and well healed before tracheostomy is advised for prolonged ventilator support.

NEUROLOGICAL COMPLICATIONS[19]

Cerebrovascular accidents manifesting as transient ischemic attacks or strokes are an ever present danger of open heart surgery. Massive cerebral or brainstem infarction or a massive bleed must always be suspected if the patient does not recover from anesthesia, and if the possibility of hypoxic brain damage is unlikely because of a smooth intraoperative and immediate postoperative course. If possible, patients who are unresponsive for 48 hours following surgery are sent for computed tomography (CT) scanning to determine the presence of organic disease or cerebral edema. Mannitol 150 mL 8 hourly intravenously, dexamethasone 4 mg intravenously 6 hourly and hyperventilation to allow a $PaCO_2$ of around 25 mm Hg are tried to counter increased intracranial pressure. Unfortunately, the patient with focal or global cerebral damage is diagnosed too late for any therapeutic measures to be effective. Risk factors for cerebrovascular accidents include the presence of preoperative carotid bruits, previous history of a cardiovascular accident or a transient ischemic episode,[20] postoperative atrial fibrillation,[21] and prolonged CPB. Patients with symptomatic carotid bruits caused by significant carotid artery stenosis have successfully undergone carotid endarterectomy with their cardiac surgery in a single operative session.

Spinal ischemia can occur after cross-clamping the thoracic aorta for repair of an aneurysm of the descending aorta. Encouraging results have been obtained by drainage of the cerebrospinal fluid and intrathecal injection of papaverine.[22]

Rarely rib resection during a thoracotomy can produce a hematoma causing compression of the thoracic spinal cord. This may present with paraplegia or a Brown-Séquard syndrome. A CT scan or a magnetic resonance imaging (MRI) can prove the diagnosis; compression should be relieved by surgery.

Box 3: Causes of cerebrovascular accident after cardiac surgery

Embolism—
- Debridement or replacement of calcified aortic valve
- Dislodgement of atherosclerotic plaque during aortic cannulation
- Introduction of air into circulation during surgery
- Atrial fibrillation
- Thrombosis of mechanical prosthetic valve
- Thrombus within the left ventricle
- Dislodgement of fragment of left atrial myxoma

Hemorrhage—
- Perioperative anticoagulation
- Hypertension

Infarction—
- Cerebral hypoperfusion while on CPB or during period of postoperative shock particularly when this occurs against a background of cerebral atherosclerosis or carotid or vertebral artery stenosis

Neuropathies in the upper limbs chiefly involving the ulnar nerve can occur following brachial plexus compression or traction injury. Recovery generally ensues in 2 months but may take as long as 9 months to a year. Box 3 lists the causes of cerebrovascular accidents following bypass surgery.

GASTROINTESTINAL COMPLICATIONS

These are rare but carry a high mortality. Ileus is often present for a few days if the gastroepiploic artery is used for revascularization. In patients with diffuse atherosclerotic disease, mesenteric ischemia may lead to the picture of an acute abdomen. This is particularly seen in hypoperfusion states and in surgery on the abdominal aorta. Acute pancreatitis possibly related to hypoperfusion may occur suddenly and can lead to rapid deterioration in the clinical state. A high index of suspicion is necessary for a diagnosis. The diagnosis should not be solely based on high serum amylase levels as these are observed in over 30% of patients undergoing CPB. Elevated serum lipase levels in conjunction with the clinical picture are of greater help in diagnosis. In patients with a low-output syndrome, which is severe or long-lasting, liver cell dysfunction is observed with marked elevation of the enzymes and a rise in bilirubin. This shock-liver syndrome improves if cardiac output, arterial blood pressure and tissue perfusion recover. Acute noncalculous cholecystitis often attributed to visceral hypotension, is a rare but important complication within the first week after surgery. It is characterized by pain and tenderness in the right hypochondrium, increase in liver enzymes and fever. The diagnosis can be confirmed by ultrasound examination. The overall mortality in these patients is over 30%,[23] the gall bladder being frequently gangrenous on explorative surgery. Gastrointestinal bleeds from acute erosions or ulcers are common, particularly in patients with a prolonged stormy postoperative course, in those who are septic, and following the use of corticosteroids. Most patients should receive sucralfate. H_2-antagonists or proton pump inhibitors are specifically indicated for high-risk patients and to counter GI bleeds. Table 1 lists the causes of some common GI complications seen after cardiac surgery.

Table 1: Common causes of gastrointestinal (GI) complications after cardiac surgery

Complications	*Common causes*
Elevated serum bilirubin—	
• Early (1–10 days)	• Hemolysis during cardiopulmonary bypass (CPB) • Shock-Liver Syndrome • Right-sided heart failure
• Late (10–90 days)	• Infection [Cytomegalovirus (CMV) or Hepatitis C virus)] • Cholecystitis
GI bleeds	• Stress gastric erosions or ulcerations • Peptic ulcer disease
Mesenteric ischemia	Low cardiac output, embolic or due to thrombi, or vascular dissection by intra-aortic balloon pump (IABP)
Pancreatitis	Hypotension, splanchnic vasoconstriction
Ileus	Use of gastroepiploic artery for revascularization; related to mesenteric ischemia
Acute noncalculous cholecystitis	Probably related to hypoperfusion

RENAL COMPLICATIONS[24]

Acute oliguric failure after open heart surgery is rare (0.7–4.3%) but carries a grave risk and a high mortality. The incidence of a quickly rising creatinine, oliguria, anuria, the need for dialysis, and the occurrence of other complications is higher when preoperative serum creatinine levels are beyond 1.7 mg/dL.[25] The occurrence of oliguric renal failure after open heart surgery often precipitates fluid overload and pulmonary edema. Early use of continuous arteriovenous hemofiltration to remove excess fluid is always indicated in these patients. Three patterns of renal failure are generally observed. The first occurs as a result of a renal insult at or soon after surgery. It is characterized by a rise in serum creatinine from the second to the fifth postoperative days. Renal function then improves and serum creatinine levels return to normal over a week. During the phase of impaired renal function, it is important to omit as far as possible all nephrotoxic drugs, in particular, nonsteroidal anti-inflammatory agents and aminoglycosides. The second pattern is characterized by a more prolonged course of acute renal failure. It occurs in patients, who, in addition to a perioperative renal insult, have hemodynamic instability and poor tissue perfusion in the initial postoperative phase. Recovery of renal function occurs after 3–4 weeks. The last and the most serious pattern of renal

failure is when complicating sepsis or a massive GI bleed is an added insult to early circulatory disturbances. This form of failure is often seen in patients who develop multiple organ failure, and carries a high mortality.

The principles of management of acute renal injury have been discussed in another chapter (see Chapter Acute Kidney Injury). We prefer to use continuous arteriovenous hemofiltration rather than hemodialysis in our patients of acute renal failure. We initiate hemofiltration early in the natural history of the disease.

INFECTIOUS COMPLICATIONS

These include wound infections, urinary tract infections, pneumonia and sepsis. Gram-negative organisms [very often extended spectrum beta-lactamases (ESBLs)] are most frequently encountered. Staphylococcal infections are also observed. A nasty nosocomial wound infection is indeed a dreaded complication of open heart surgery. Healing may be protracted and difficult. In the worst scenario, the sepsis syndrome with multiple organ failure results. At times local dehiscence may cause a total separation of the sternal wound with exposure of the mediastinum. Wound infections often necessitate prolonged ventilator support. Healing of infected wounds is doubly difficult in patients with poor pump function. The risk of nosocomial wound infection in the unit is significantly increased if there is even one patient with severe wound infection, who continues to need prolonged critical care within the unit.

Local attention to the wound should be left to the surgical team. Appropriate cultures of discharge from the wound should guide systemic antibiotic therapy. Mediastinitis, mediastinal abscess, pleural effusion (unilateral or bilateral), empyemas may all complicate a bad sternal wound infection. These need to be diagnosed and surgically treated. Wound infections are further discussed in a separate chapter (see Section Surgical Infections in the Intensive Care Unit).

INFECTIVE ENDOCARDITIS

Prosthetic valve endocarditis is a rare complication of cardiac surgery, occurring in 2–4% of patients. Half of these are classified as early (<60 days after surgery), and half as late cases (>60 days following surgery). Early endocarditis is most often due to *Staphylococcus aureus (S. aureus)*,[26] and then in descending order of frequency, to Gram-negative bacilli, diphtheroids and fungi. Late endocarditis is more often due to the streptococcus species, and the microbiologic spectrum causing infection is similar to that observed in native valve endocarditis. Mechanical valves typically show a ring abscess or a myocardial abscess, whereas infected porcine valves show stenosis or regurgitation. Antibiotic therapy depends on the organisms grown on blood culture. The regime against early endocarditis should include vancomycin to cover methicillin-resistant staphylococci. Indications for surgery include prosthetic valve dysfunction, myocardial abscess, perivalvular infection and abscess, persistently positive blood cultures, relapse after antibiotic therapy, embolic episodes and cardiac dysfunction or failure.[27]

PERIPHERAL VASCULAR COMPLICATIONS AND PULMONARY EMBOLISM

Embolic or thrombotic occlusion of vessels in the limbs, (particularly the lower limbs), may occasionally occur. Thrombectomy or revascularization surgery of the lower limbs may be necessary to salvage the limb. Heparinization is indicated.

Deep vein thrombosis of the calves is a frequent complication. Rarely this may result in a massive pulmonary embolism. Sudden hypotension with a shock-like state occurring after the sixth day of surgery should suggest this complication. Major pulmonary embolism can be easily proven by a high-resolution computed tomography (HRCT) pulmonary angiography. Heparin in full doses, 5,000 units intravenously to start with, followed by 1,000 units/hour, to keep the PTT to 2–2.5 times normal should be given. Most intensivists prefer to use enoxaparin (low molecular weight heparin) 0.6 mg subcutaneous 12 hourly in preference to unfractionated heparin. Streptokinase is avoided in view of major surgery in the very recent past.

MULTIPLE ORGAN DYSFUNCTIONS

This is a rare but dreaded complication of open heart surgery. It can occur very rarely because of a systemic inflammatory response syndrome initiated during CPB. In these cases, it manifests initially with mild to moderate degree of acute lung injury (ARDS). Progressive multiple organ dysfunction is more likely to occur if the patient has suffered a myocardial insult resulting in a prolonged period of poor perfusion, during or after surgery. Provided there is scope for recovery of myocardial function, and there is no complicating sepsis, multiple organ failure in this situation does not carry the grim prognosis forecast by many workers in the West. We have had three patients who suffered an insult causing severe hypoperfusion before, during and after bypass surgery. They developed severe multiple organ failure involving all organ systems for more than 2 weeks, but still made a complete recovery. If severe sepsis complicates the above picture, then the prognosis is extremely grim, and death invariably results.

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SECTION

17

The Immunocompromised Patient

- The Immunocompromised Patient

CHAPTER 63

The Immunocompromised Patient

INTRODUCTION

Immunocompromised patients who get infections and are seriously ill under intensive care are under grave risk and have a far greater mortality as compared to patients with a normal immune status. It is almost certain that in years to come intensive care units (ICUs) will be populated by an increasing number of immunosuppressed or immunocompromised patients. The occurrence of infection in compromised patients reflects the interaction between these patients' immune defense system and their endogenous and exogenous microbial environment. It is impossible to discuss in detail the normal immune defense mechanisms in this chapter, but a brief outline of immune responses that help fight infection is of basic importance to doctors working in ICUs. This is because specific defects in the immune defense system predispose immunocompromised patients to certain specific infections. Unfortunately in acutely ill patients it is not always possible to quickly identify these specific deficits, nor is it advisable to perform elaborate tests to do so.

BASIC HOST DEFENSE MECHANISMS

Host defense mechanisms are complex interacting systems. These mechanisms chiefly include—

Inflammatory Response

Circulating phagocytes and, in particular, the neutrophils form the most important part of this inflammatory response. A wide variety of bacteria as well as fungi are capable of being ingested, digested and killed by neutrophils. Severe neutropenia strongly predisposes a patient to infection by Gram-negative and Gram-positive bacteria, especially *Pseudomonas aeruginosa*, *Klebsiella, Enterobacter* species, *Escherichia coli* and *Staphylococcus aureus*. Fungal infections, notably of the *Aspergillus*, *Candida* and *Mucor* species are also observed in neutropenic patients.

Complement System

The complement cascade especially C3a and C5a together with other mediators promotes and directs phagocytes to the areas of inflammation. If the organisms within the area of infection have been opsonized by complement or antibodies, phagocytosis and destruction of the organism are facilitated. A complement deficiency therefore also predisposes to bacterial infection, particularly of the *Neisseria* species.

Reticuloendothelial System

Circulating micro-organisms are cleared from the bloodstream by tissue phagocytes derived from circulating monocytes. The most important tissue phagocytes include the Kupffer cells in the liver, phagocytes in the spleen, lymph nodes, lung (alveolar macrophages), kidney (mesangial cells) and brain (microglial cells). Suppression or poor function of the reticuloendothelial system can lead to bacteremia and sepsis from exogenous and/or endogenous microbial flora.

IMMUNE RESPONSE

The B-cell lymphocyte response to infection is the production of antibodies (IgG, IgA, IgM, IgE) and the T-cell lymphocyte response leads to a cell-mediated immune defense. Humoral defense through antibody production and cell-mediated immunity are closely interrelated, inter-reactive and interdependent.

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Humoral deficiency exposes the patient at times to overwhelming infection, particularly to *Streptococcus* and *Haemophilus influenzae pneumonia*.

Cell-mediated immune deficiency often renders the patient susceptible to protozoal, fungal, viral and rarer bacterial infections. Infections with *Pneumocystis*, *Toxoplasma gondii, Cryptococcus neoformans*, mycobacterial infections [tuberculosis and *Mycobacterium avium*-complex (MAC) infections], infections by the *Legionella* species, and by *Listeria monocytogenes* are observed in these patients. Viral infections include infections due to cytomegalovirus (CMV), herpes simplex and herpes zoster virus.

The following groups of immunocompromised patients are often seen in ICUs.[1]

Solid Organ Transplant Recipients

Most common in this group are patients who have received a kidney and liver transplant. In western countries, patients with heart, lung and pancreas transplants are also additionally seen. These patients are all immunosuppressed, as they must have lymphocyte depletion so that the transplants survive. They demonstrate an increase in suppressor T-lymphocytes and limited T-cell cytotoxic activity. In addition, they suffer from the effects of prolonged corticosteroid administration and the use of cyclosporine. Infection, sometimes sudden and overwhelming, is an important and dreaded complication in all organ transplant recipients. Different infections generally occur in different time frames (early or late after transplant) and this serves as a rough aid in diagnosis (see Chapter Critical Care of the Transplant Patient).

Hematopoietic Stem-Cell Transplant Recipients

Hematopoietic stem-cell (HSC) transplants are increasingly used as therapy for various hematological malignancies, hemoglobinopathies, immunodeficiency disorders and even for solid tumors. Autologous stem-cell transplant is associated with neutropenia as the primary immune defect. Allogeneic transplants lead to a broader range of immune defects with more wide-ranging complications.

Patients with Malignant Disease

Advanced malignancy leads to immunosuppression; lymphomas and, in particular, Hodgkin's lymphomas are also associated with immunosuppression of the cellular immune reaction.

Patients on Corticosteroid Therapy

Corticosteroids are amongst the most frequently used drugs in medicine, and the doctor in a critical care unit may be unaware of the history of corticosteroid ingestion by an acutely ill patient admitted as an emergency. Corticosteroids suppress the immune response and mask the underlying pathology and inflammation. Patients on maintenance steroid therapy for long periods of time may easily go into an acute adrenal crisis in the presence of overwhelming infection, if the attending doctor is unaware of the history of steroid ingestion, and if the dose of corticosteroids is not suitably increased during such a crisis.

Patients on Antimitotic Drugs

All antimitotic drugs are immunosuppressive and therefore predispose to infection. Cyclophosphamide and nitrogen mustard affect cell replication and bone marrow function. Antimetabolites affect and interfere with purine and pyrimidine metabolism, and prevent an adequate cellular immune response to infection.

Splenectomized Patients

These patients have an altered immune function. Immunoglobulin M (IgM) production in response to bacterial antigen is markedly slow, and patients are particularly prone to fulminant infections by *pneumococcus* and other encapsulated organisms.

Immune Suppression in Chronic Disease

This is one of the most important groups encountered in our ICUs, and includes patients with liver cirrhosis, liver cell failure, chronic renal failure, patients on chronic hemodialysis, severe diabetics, alcoholics and those with myeloproliferative disorders. In our country as well as in other third-world countries, poor nutrition is a frequent background factor against which many acute infections evolve. These patients are prone to acute infections and are more likely to die of these infections in ICUs.

Immune Suppression in Human Immunodeficiency Virus Infection

According to the WHO report in 2011, about 34 million people worldwide are infected with the human immunodeficiency virus (HIV), with nearly 90% of the infected residing in developing countries.[2] In 2009, it was estimated that 2.4 million people were living with HIV in India, which equates to a prevalence of 0.3%. While this may seem low, because India's population is so large, it is third in the world in terms of the greatest number of people living with HIV.

HIV causes depletion in T4 lymphocytes with a marked deterioration in cell-mediated immunity. The most serious feature of acquired immunodeficiency syndrome (AIDS) is the occurrence of infectious complications, particularly by opportunistic organisms.

APPROACH TO THE ACUTELY ILL IMMUNOCOMPROMISED PATIENTS

The following features are worthy of note—

- Acute infections in immunocompromised individuals can be sudden, overwhelming and rapidly fatal.
- The clinical manifestations of such infections are not usually of the same intensity and degree as compared

to those in patients with normal immune mechanisms. Diagnosis is doubly difficult because of the paucity of signs and the short time available between the onset of symptoms and possible death.

- Complications due to noninfective causes may interfere with the diagnosis of actual infection. For example, fluid overload, atelectasis and pulmonary infarction may cast lung shadows on an X-ray chest that may be mistaken for infection.
- The clinician must recognize that the immunosuppressed patient is exposed to, and is likely to be infected by two groups of microbial pathogens—
  - The usual pathogens which can also afflict immunocompetent patients.
  - Opportunistic organisms which invariably affect immunosuppressed patients only.
- The nature and specificity of infection to an extent is related to the degree of immunocompromised state. For example, in HIV patients, computerized tomography (CT) enhancing discrete brain lesion is more likely to be due to toxoplasmosis or central nervous system (CNS) lymphoma, whereas similar lesions in solid organ transplant patients are chiefly caused by filamentous fungi (e.g. *Aspergillus*). Also *M. avium* complex lesions occur more frequently in advanced AIDS, rather than in solid organ, hematologic transplant or in patients on corticosteroids.
- There are characteristic time windows during which specific pathogens generally cause infections in immunocompromised patients. This is elaborated upon later in this chapter.
- Early diagnosis is imperative as the likelihood of quick deterioration and death is often seen. An aggressive diagnostic methodology must prevail. Tissue diagnosis whenever possible obviates the need for the use of dangerous drugs.
- Treatment of acute infections in immunocompromised individuals in ICUs should be prompt. It is often empirical and tailored to counter more than one possible infection depending on the clinical picture, and on the background against which this picture evolves. Therapy for immunosuppressed patients often involves the use of drugs directed against opportunistic organisms, and is often different from therapy in acute infections afflicting patients with normal immunological responses.

ACUTE OR CRITICAL INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

In a critical care setting, infections in immunocompromised individuals generally present in the following manner—

- Fever with neutropenia.
- Sepsis and septic shock.
- Pneumonia.
- Mucocutaneous manifestations—
  - Stomatitis.
  - Esophagitis.
  - Skin rashes.
  - Discrete skin lesions.
- Disseminated tuberculosis.
- Meningitis and CNS infections.
- Disseminated syndromes involving more than one organ system.

Pyrexia of Unknown Origin with Neutropenia

This is generally observed in patients with myeloproliferative disease, lymphoma and cancers after aggressive chemotherapy. Severe neutropenia results in a loss of phagocytic function leading to infectious complications. Associated B-cell and T-cell dysfunction further contributes to these complications. The risk of infection depends on the degree and duration of neutropenia. The infection rate is significantly increased if the neutrophil count is less than 1.0×10^9/L and is highly probable, if it further falls to 0.5×10^9/L. Infection invariably results if the duration of severe neutropenia is more than 10 days. Many infections result from the patient's own endogenous flora (i.e. from the skin, gut and lungs); approximately half of the infections are nosocomial in origin. In our unit, the organisms most frequently involved are the Gram-negative organisms such as the *P. aeruginosa*, *Klebsiella*, *Enterobacter*, *Serratia* and Gram-positive organisms. *S. aureus* (including the methicillin resistant) and *Staphylococcus epidermidis* are uncommon infections in our unit; though they form important pathogens in other CCUs, particularly in the West. Invasive fungal infections due to *Candida, Aspergillus* and *Mucor* species are increasingly observed.

The organism causing fever in patients with severe neutropenia is microbiologically identified in less than a quarter of cases. In another quarter, the clinical symptomatology suggests an infection, though the nature and site of infection again remain unproven, and in half or more patients the fever remains of unknown origin. Thus, in many such patients, a complete physical examination, basic radiological, ultrasound tests, blood tests including cultures of blood, urine and body secretions are all negative. A CT of the chest and abdomen should always be done in these patients. Pneumonia not evident on an X-ray chest may show up on a CT chest and a CT abdomen may reveal a focal abscess that would otherwise go unrecognized. It is therefore imperative that in patients with severe neutropenia (to the extent described above), with fever (defined as a single oral temperature of 38.3°C or 38°C for at least one hour), empiric antibiotic therapy should be promptly commenced after relevant blood tests, culture of blood, urine other body secretions and a chest X-ray have been done. One should never await results. We generally prefer to cover Gram-negative organisms (in particular *Pseudomonas*) with a third-generation cephalosporin or a piperacillin derivative, plus an aminoglycoside. Gram-positive cover is provided with intravenous (IV) amoxycillin + clavulinic acid. If there is a strong suspicion of methicillin resistant *Staphylococcus* causing infection, vancomycin is substituted for amoxycillin + clavulinic acid. Further modification in antibiotic coverage depends on results of tests, and on response to therapy.

We also administer the granulocyte stimulation factor daily to help increase the leucocyte and neutrophil count to safe levels.

Patients with a pyrexia of unknown origin (PUO) and neutropenia who fail to respond within 2 days of a broad-spectrum antibiotic cover should in addition be given amphotericin B to cover a possible fungal infection. Amphotericin B is used even earlier if the patient deteriorates quickly, if there is a background known to significantly increase fungal super-infection (as in patients on prolonged corticosteroid therapy), or if pleuritic pain, cough, hemoptysis point to infection in the chest and a high-resolution computerized tomography of the chest is suggestive of a possible fungal infection.

Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy should be performed only if the patient fails to respond to the above management protocol. This is because opportunistic infections such as *P. jirovecii* are rare in patients with fever and neutropenia, except in patients with underlying lymphoma or in those on long-standing corticosteroid therapy.

Surgical biopsy is very rarely indicated, when for example, infiltrates in the lung persist in spite of therapy and the patient is deemed fit to withstand the surgical procedure.

The mortality of patients with fever and severe neutropenia is significantly reduced with the empirical therapy described above. A febrile neutropenic patient should be watched closely and should avoid external contact with other individuals.

Sepsis and Septic Shock

Sepsis or septic shock is probably the most dreaded complication in immunocompromised individuals. The source and nature of sepsis is at times obvious, and at times remains undetermined in spite of all investigations. The important sources of sepsis are—

- An abscess or infected hematoma anywhere within the body for which the patient requires critical care.
- *Intra-abdominal sepsis* The most frequent cause of this is a perforated gut due to any etiology, with peritonitis. A delayed diagnosis and late surgery are sure pointers to a very high mortality in spite of excellent surgical techniques and good postoperative care. If the source of infection within the peritoneal cavity cannot be completely eradicated, death is inevitable.
- Sepsis is sometimes related to a community-acquired bacterial infection—chiefly pneumonia.
- Sepsis also follows upon opportunistic infections, in particular, viral and fungal infections.
- An immunocompromised patient may be admitted to an ICU for trauma or following surgery. These patients are extremely prone to nosocomial infections. Nosocomial pneumonia, and nosocomial sepsis through central lines, catheters, ventilator tubings and nebulization equipment are frequent, and carry a forbidding mortality. Sepsis may arise from the overgrowth of pathogenic bacteria in the gut and their translocation into the systemic circulation.
- As mentioned earlier, the source and nature of sepsis at times remains undetermined.

The diagnosis of sepsis and septic shock has been discussed in an earlier chapter. In immunocompromised patients, fever and leukocytosis may not be as high as in patients with a normal immune system. In fulminant cases, hypothermia and leucopenia may be observed. Physical signs are subtle, and may be easily missed or ignored. Deterioration is often rapid, with a quick onset of multiple organ dysfunction and failure.

The principles of management discussed under septic shock are applicable to immunocompromised patients. It needs to be stressed that however ill the patient, a localized source of infection if accessible should be promptly dealt with surgically. An abscess simply must be drained, and abdominal sepsis must be surgically tackled. The choice between aspirating a localized abscess under ultrasound or CT guidance, or incising and draining it should be left to the surgeon.

It is often necessary to start appropriate empiric antibiotic therapy promptly, after collection of secretions and of blood for culture has been done. We generally start with amoxycillin + clavulinic acid 1.2 g 8 hourly intravenously to counter possible coccal infections, a third-generation cephalosporin like ceftazidime 2 g intravenously 8 hourly which acts against Gram-negative infections including *Pseudomonas aeruginosa*, and an aminoglycoside which also acts against Gram-negative infections. Any antibacterial regime against Gram-negative infections should preferably include a combination of two antibiotics to provide wide coverage.

In nosocomial infections, the choice of antibiotics is governed by the nosocomial organisms most frequently encountered in a particular intensive care setting. In our unit, *P. aeruginosa*, *Klebsiella* and *Enterobacter* are the common organisms responsible for nosocomial infections. There is a marked increase in the incidence of the extended spectrum beta-lactamase (ESBL) producing organisms in ICUs in India, resistant to most antibiotics. The regime recommended is a carbapenem plus an aminoglycoside. When there is a possibility of a staphylococcal infection, or in very ill patients, or in those who show no response within 36 hours of starting the above standard regime, we add vancomycin 500 mg 6 hourly intravenously to the management protocol.

In certain clinical settings the standard regime may need to be modified—

- If culture reports suggest that the patient is colonized and probably infected by an organism resistant to the regime chosen, or if the patient is admitted to a unit where an uncommon, resistant organism is known to be responsible for frequent infections, a drug acting against such an organism is added or substituted in the regime.
- If the clinical situation suggests an associated anaerobic infection (as in abdominal sepsis, perianal or perirectal sepsis, or in sepsis following aspiration of gastric contents), the addition of metronidazole 500–750 mg intravenously

every 8 hours, or clindamycin 600 mg intravenously 6 hourly, or penicillin 2 mega units intravenously 4–6 hourly, is warranted.

- If sepsis is thought to be related to central lines, IV vancomycin 500 mg 6 hourly should always be included in the regime.
- If *H. influenzae* is likely to be the incriminating organism, it is best to include a third-generation cephalosporin (if not used), or use cefuroxime acetate 1.5 g intravenously every 8 hours.
- Ordinarily antifungal therapy is not included initially in the standard regime except when there is strong clinical evidence, right from the outset, of a fungal infection. However, if an immunocompromised patient with sepsis or septic shock fails to improve within 48 hours on an antibacterial regime outlined above, antifungal treatment with amphotericin B or an Echinocandin is added to the therapy. In patients with cancer, in those immunosuppressed by antimitotic drugs, or in those immunosuppressed patients who have received broad-spectrum antibiotics for prolonged periods of time and who suddenly deteriorate, many would prefer to initiate antifungal therapy promptly. In patients with sepsis and severe granulocytopenia, who fail to improve on antibacterial broad-spectrum antibiotics, or those who improve initially but then suddenly deteriorate, a fungal infection is strongly suspect, and lyophilized amphotericin B or any other suitable antifungal agent should be added empirically to the therapeutic regime (see earlier section on PUO with neutropenia).
- In patients with cellular immune defects, antimicrobial therapy must consider coverage of *Listeria monocytogenes* (ampicillin 2 g every 4 hours and gentamicin). Fungal infections (chiefly *Candida* and *C. neoformans*) and viral infections (CMV and herpes virus) are also to be suspected in this situation.

There are no firm and objective guidelines regarding the duration of antibiotic treatment of sepsis in immunocompromised patients. Antibiotics should be continued till sepsis is well controlled—generally treatment lasts for at least 7–12 days, and often longer. If possible, the serum antibiotic concentration of all patients with sepsis, and, in particular septic shock should be monitored. Dose modifications may therefore be necessary, particularly in the presence of hepatic or renal dysfunction induced by the disease, by shock or by previous treatment.

The role of corticosteroids in sepsis has been discussed in the Chapter Sepsis and Septic Shock. Immunoglobulin infusions or infusions of complement or transfer factor to augment the immune response are of dubious clinical efficacy. However, the use of granulocyte colony stimulating factor (5–10 μg/kg per day) in such patients is often rewarded by an increase in the granulocyte count after a few days. A satisfactory granulocyte response may well turn the tide in the patient's favor.

Pneumonia and Pulmonary Infections

Infections in immunocompromised patients frequently take the form of pneumonia. In these patients, pneumonia very frequently results from the usual bacterial flora prevailing within the community. The commonest community-acquired pneumonia in India (as in other countries) is due to the *S. pneumoniae*. In older, particularly immunocompromised individuals, Gram-negative infections are frequent. In our country, as well as in all third-world countries where tuberculosis is common, a flare-up of this disease always needs to be considered. The diagnosis may not be easy as many of these patients produce little or no sputum for examination.

Immunocompromised patients, in contrast to patients who are immunocompetent, are however increasingly prone to opportunistic infections. In AIDS, pneumonia due to *Pneumocystis* is frequently observed when the CD4 lymphocyte count is less than 200/mm^3. *P. jirovecii* infection can also occur in lymphomas, leukemias, myeloproliferative disorders, organ transplant recipients, in patients on corticosteroid therapy and rarely in patients with rheumatoid disease on methotrexate therapy. Other opportunistic organisms causing pneumonia include the CMV and the herpes virus, *M. avium intracellulare*, protozoa, helminthes (Strongyloidosis) and fungi. Not uncommonly, more than one opportunistic organism is present in the same individual.

Finally, immunocompromised patients admitted to an ICU for noninfectious conditions (trauma and surgery) are especially prone to nosocomial pneumonia.

There are some noteworthy features in relation to pneumonia in immunocompromised patients—

- Pneumonias constitute a major cause of morbidity and mortality in diverse immunosuppressed populations and therefore pose a problem of enormous magnitude. In one large reported study of renal transplant patients, pneumonia occurred in 20% of patients and accounted for 50% of deaths.[3] Similarly in patients with lymphomas, pneumonia is the commonest infection causing death.[4] Interstitial pneumonia is reported to occur in 55% of bone marrow transplant recipients who survive for 30 days after transplantation, and carries a mortality of 60%.[5]
- In many patients, the symptoms are few, and there is a paucity of physical signs. In neutropenic patients, physical signs are virtually absent. An increase in the respiratory rate is probably the only important sign which may be observed. Radiological shadowing in neutropenic patients is barely noticeable and may even be absent due to the total lack of neutrophilic response in such patients.
- Pneumonias due to bacterial infections can be multilobar. Acute lung injury [acute respiratory distress syndrome (ARDS)] is more often observed in immunocompromised patients under the above circumstances. Similarly, multiple organ dysfunction, failure and death are more frequently observed.

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Box 1: Noninfective pulmonary infiltrates or "shadows" in the immunocompromised host

- Pulmonary edema
- Pulmonary hemorrhage
- Acute respiratory distress syndrome
- Pulmonary embolism
- Drug-induced pulmonary disease
- Leukoagglutinin reaction
- Opportunistic neoplasms (lymphoproliferative disorders and Kaposi's sarcoma)
- Recurrence of a tumor, of a lymphoma, or of a leukemia in the lungs
- Immune-mediated disorders—
  - Acute rejection after lung transplant
  - Obliterative bronchiolitis
- Nonspecific inflammation

- A quick diagnosis allows specific therapy to be promptly instituted and improves patient survival. In renal transplant patients, a mortality of 21% was noted in those patients where a specific diagnosis was made within 5 days of the illness. In contrast, the mortality rate was 65% in patients who were diagnosed after 5 days of illness.[3]
- Each ICU must have a protocol or a plan of approach for dealing with an immunocompromised patient admitted with fever and pulmonary infiltrates. Good patient care in these patients necessitates a team approach which should however be orchestrated by a single individual in charge of patient care. It is unfortunate and sad that many microbiological and pathological laboratories in our country (outside large metropolitan cities) are ill-equipped to diagnose opportunistic infections, particularly *Pneumocystis,* viral infections and infections caused by rarer microbes—chiefly *Legionella*, *Mycoplasma* and *Nocardia*. Management protocols in third-world countries should therefore take into account the facilities available for investigations.
- Fever with pulmonary infiltrates in an immunocompromised individual is not always related to infection. It is vital to be aware of this fact. Noninfective causes of pulmonary "shadows" or infiltrates include pulmonary edema, pulmonary hemorrhage, pulmonary embolism, drug-induced pulmonary disease, and ARDS and opportunistic neoplasms (lymphoproliferative disorders, Kaposi's sarcoma). Other noninfective lesions include recurrence of underlying tumor, lymphoma, leukemia, within the lungs, immune-mediated disorders (acute rejection after lung transplant, obliterative bronchiolitis after lung transplant or after an allogenic stem-cell transplant), and nonspecific focal inflammation (Box 1).

Clinical Approach to Diagnosis of Fever with Pulmonary Infiltrates in Immunocompromised Patients

Knowledge of the background disease Patients with cell-mediated immune deficiency, e.g. HIV infection, prolonged corticosteroid therapy, Hodgkin's or other lymphomas, and those with organ transplants, are prone to infections by *M. tuberculosis*, *P. jirovecii*, CMV, other herpes viruses, *Cryptococcus*, *Nocardia* and *Legionella*. On the other hand, patients whose main defect is a severe granulocytopenia are prone to Gram-negative infections, staphylococcal and fungal infections (*Aspergillus, Mucor* and *Candida*).

In organ transplant patients, the time of onset after transplantation may be of diagnostic assistance. CMV pneumonias occur from 1 to 4 months after renal transplantation, but are relatively rare prior to or after this period.[3] Pneumonias occurring within the first 3–4 weeks after a transplant are almost never due to an opportunistic organism, but result from the usual bacterial pathogens causing post-operative pneumonias in surgical patients. Between 1 and 4 months after the transplant, besides the CMV, infections due to *Nocardia*, *Pneumocystis* and fungi should be kept in mind. After 4 months, patients who have normally functioning grafts, and who are on minimal immunosuppression, are prone to the usual community-acquired infections. Those with poorly functioning grafts, who require intensive immunosuppression, remain susceptible to the opportunistic infections stated above.

In the early part of the natural history of lymphomas, the patient is at greater risk for community-acquired pneumonias. As the disease progresses and particularly with repeated therapy, the patient is at greater risk for opportunistic pathogens.

Epidemiological clues should always be sought. In our country and in other third-world countries, depressed cell-mediated immunity is most likely to exacerbate or result in infection with *M. tuberculosis*. However, residence and exposure in areas endemic to fungi such as *Histoplasma capsulatum* or *Coccidioides immitis* could predispose to histoplasmosis or coccidioidomycosis.

Infiltrates due to noninfectious causes also have a predictable time for making their appearance. Patients treated for acute myeloblastic leukemia may develop interstitial pulmonary infiltrates. When these infiltrates occur within 4 days of a fall in the white blood cell count, they are suggestive of a leukemic cell lysis pneumopathy.[6] The mechanism of infiltrates and alveolar damage in this syndrome is perhaps related to the lysis of interstitial and alveolar blast cells. A pattern of pulmonary edema developing within minutes to hours of transfusion of blood or other blood products raises the possibility of a leukoagglutinin reaction.[6] On the other hand, pulmonary shadows (sometimes localized), may be related to pulmonary edema produced by overhydration, poor left ventricular function, or a capillary leak as in early acute lung injury (ARDS).

Bleomycin is the commonest drug responsible for interstitial infiltrates after the patient has received a cumulative dose of 150 mg of the drug. However, idiosyncratic reactions may occur with much smaller doses. Other antimitotic drugs, particularly methotrexate and busulfan, can also result in interstitial infiltrates.

Table 1: Differential diagnosis of fever and pulmonary infiltrates in the immunocompromised patient, based on radiological signs and onset of symptoms

Chest X-ray	*Symptoms*	
	Acute onset	*Subacute or Chronic onset*
Consolidation	• Bacterial • Thromboembolic • Hemorrhage	• Fungal • Nocardial • Tuberculosis
Peribronchial + alveolar shadowing; interstitial infiltrate	• Pulmonary edema • Leukoagglutinin reaction	• Viral • *P. jirovecii* • Radiation • Drug induced
Nodular infiltrate	• Bacterial • Pulmonary edema	• Tumor • Fungal • Nocardial • Tuberculosis

The mode of onset and the tempo of progression These often provide crucial clues in the diagnosis. Their value is enhanced if the above features are considered in association with radiological findings (Table 1). An acute onset over 24–48 hours is suggestive of a conventional bacterial infection, or certain noninfectious causes such as pulmonary edema, pulmonary hemorrhage, pulmonary embolism or a leukoagglutinin reaction. A subacute onset over a few days or weeks suggests tuberculosis, *Pneumocystis*, viral, fungal or *nocardial* infections. The same presentation may however also be observed with certain noninfectious causes such as drug-induced pneumonitis, radiation pneumonitis, or the recurrence of a tumor against the background of a mitotic disease.

Physical examination Physical examination may occasionally provide valuable clues. In sophisticated ICUs with high-technology equipment, physical examination tends to be perfunctory; this should never be so. Repeated clinical examination might reveal clues, which machines and elaborate investigations fail to detect. The features enumerated below are merely illustrative of the importance of a careful physical examination—

- Tachypnea in an immunocompromised patient, particularly in the absence of high fever is indicative of sepsis, pneumonia or acidosis. Physical signs in the chest may or may not be evident; an absence of signs on percussion or auscultation is often observed in these patients.
- Skin lesions are occasionally present in cryptococcal, nocardial and candidal infections. They take the form of minimally painful or asymptomatic macules, papules or nodules, which on biopsy provide the correct diagnosis, thereby obviating the need for invasive diagnostic procedures. Pyoderma gangrenosum is occasionally observed in infections with *P. aeruginosa*, and very rarely with other Gram-negative infections.
- A careful search for enlarged lymph glands can be rewarding. Lymphadenopathy strongly suggests a tuberculous infection in our country, either due to *M. tuberculosis* or in AIDS patients to a possible infection with *M. avium-intracellulare*. An underlying lymphoma, presenting with an obscure pneumonia, has been occasionally diagnosed following the biopsy of a nondescript clinically palpable lymph node.
- Ocular examination is important as ocular findings are common with disseminate CMV infection. The retina shows hemorrhages and yellowish-white exudates. Similar ocular findings have been noted in toxoplasmosis and occasionally in candidiasis, and aspergillosis.
- Examination of other systems is of crucial importance. Hepatosplenomegaly with lymphadenopathy may point to an underlying lymphoma or a myeloproliferative disorder. It is also commonly observed in disseminated hematogenous tuberculosis and toxoplasmosis.
- Neurological examination may reveal subtle symptoms and signs suggesting meningitis or a focal neurological lesion. Brain abscess is common in nocardial infection, cryptococcal infection and in disseminated disease due to *M. tuberculosis* (see Chapter Neurological Problems).
- Radiological Investigations in patients with pulmonary infiltrates generally do not allow a definitive etiological diagnosis to be made. Nevertheless, a study of serial chest X-rays, when combined with an analysis of the mode of onset and the progress of the disease, often help in limiting the diagnostic possibilities.

Focal or multifocal consolidation of short duration (less than 48 hours) seen on a chest X-ray is invariably due to an acute bacterial infection. Slowly progressive consolidation with a subacute or chronic history favors tuberculosis, nocardial or fungal infections.

Interstitial infiltrates spreading outwards from the hilar area and evolving in a subacute or chronic manner, suggest *Pneumocystis*, viral or drug-induced infiltration, or may be due to lymphangitic carcinomatosis. Acutely evolving interstitial infiltrates suggest pulmonary edema or a leukoagglutinin reaction.

Acute nodular localized alveolar consolidation or localized nodular infiltrates suggest pulmonary edema or bacterial bronchopneumonia. Nodular infiltrates which are subacute or chronic and slow in evolving could be tuberculosis, fungal or nocardial in etiology. Such infiltrates could also be due to the recurrence or spread of an original tumor.

These radiological observations are not sacrosanct, and as mentioned at the outset, an exact diagnosis can never be made by the mere description of shadows on a chest radiograph. The overall picture has to be considered.

It must be stressed that HRCT of the chest must always be done in immunocompromised patients with possible pneumonia. The CT generally gives much more information than a chest X-ray and may suggest a possible diagnosis not entertained on a mere viewing of the chest X-ray. For example,

Table 2: Likely respiratory pathogens in specific immunocompromised-host categories based upon presenting radiographic pattern

	Diffuse interstitial-alveolar	*Lobar-segmental*	*Reticulonodular*	*Discrete nodule*
Chemotherapy-induced granulocytopenia	Cytomegalovirus (CMV) (ALL)	Bacterial	-	Bacterial, *Aspergillus* Other mycelia
Bone marrow transplant	*P. jirovecii,* CMV, Respiratory syncytial virus (RSV), Influenza virus, Adenovirus	Bacterial, *Legionella* RSV Influenza virus	*Nocardia*	Other mycelia *Aspergillus* *Nocardia*
Solid organ transplant	CMV *P. jirovecii* Influeza	Bacterial Influenza virus	*Nocardia* *M. Tuberculosis*	*Aspergillus* Other mycelia
HIV-1	*P. jirovecii* CMV	Bacterial *Rhodococcus* *Cryptococcus*	*P. jirovecii* Histoplasmosis	Bacterial *Cryptococcus*

it may reveal cavitative lung disease or show features suggestive of *Aspergillus* infection, not evident on an X-ray of the chest. Table 2 gives the likely pathogens in specific immunocompromised states based on imaging (X-ray chest and HRCT chest) findings.

Management Protocol

This should be organized and planned depending on the facilities present in an ICU, and the degree of sophistication of the pathology and microbiology departments of the hospital. Routine investigations include a blood count, blood chemistry, blood culture, sputum examination (Gram stain and acid-fast stain), sputum culture, X-ray chest and often an HRCT chest. A Gram stain of the sputum at times provides a direction to appropriate therapy. In some patients, nebulization with hypertonic saline helps to obtain a satisfactory sputum sample (Flowchart 1).[7]

Empiric therapy should be started without awaiting results of blood and sputum tests. Therapy could be later changed, if the results so necessitate. The protocol we use in an acutely ill immunocompromised patient is as follows—

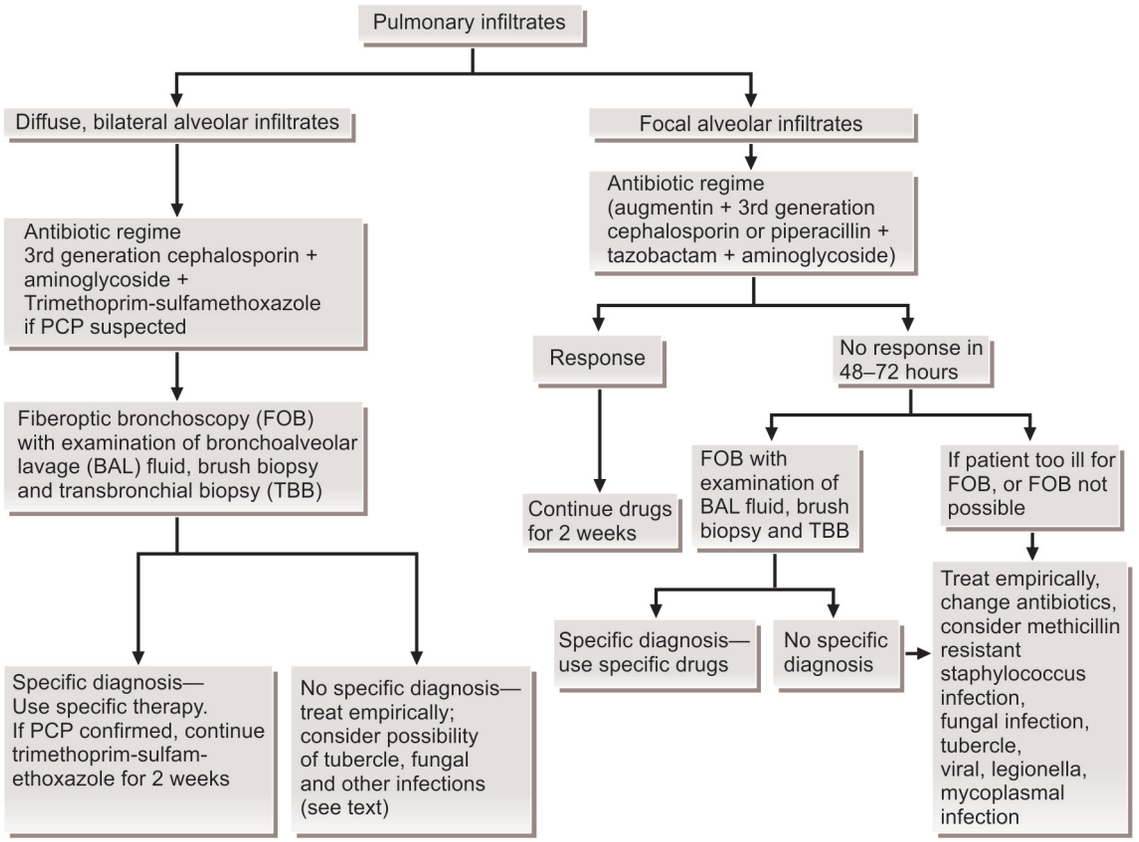
- If the patient presents with a focal alveolar infiltrate or consolidation, we use intravenous augmentin plus a third-generation cephalosporin, like ceftazidime plus an aminoglycoside, or alternatively use other broad-spectrum antibiotics that counter Gram-positive and Gram-negative infections, as outlined in the section on sepsis. The choice of the antibiotic regime depends on the possible nature of the organisms suspected in a given individual. Nosocomial pneumonias in immunocompromised patients should include a carbapenem like meropenem 1 g 8 hourly plus an aminoglycoside, in view of a marked increase in ESBL producing organisms. Many patients with *P. aeruginosa* infection are now resistant to carbapenems and other antibiotics. One is left with the use of Colistin with its loading dose (9 MIU) and maintenance dose of 2–3 million units IV 8 hourly as the only resort. The maintenance dose of Colistin must be adjusted according to the creatinine clearance of the patient. Since Colistin must never be administered alone, it is combined with a carbapenem which is given as a prolonged infusion. In pneumonia associated with severe neutropenia, particularly in those who have pleuritic pain, cough, hemoptysis and whose HRCT is compatible with an *Aspergillus* infection, we would add amphotericin B or voriconazole to the regime of broad-spectrum antibiotics on an empiric basis. If the patient responds to the above treatment, the antibiotic course is continued for a period of 2 weeks or even longer.

If the patient does not respond within 48–72 hours or if the disease progresses, it is best to do a bronchoalveolar lavage with a careful examination and culture of the lavage fluid. Whenever possible, brush biopsies of the involved areas by standard accepted techniques are recommended. A transbronchial biopsy of the lesion, if thought appropriate, can be done during the same procedure. The biopsy material is processed promptly for staining of the organisms, histopathology and cultures. The following etiological agents are diagnosed by these techniques—

- Gram-negative or Gram-positive infections.
- *M. tuberculosis* It is amazing how often this diagnosis would have been missed or would not have been seriously entertained if the above diagnostic procedure was not performed.
- Other rare infections, for example, *nocardial* infections.
- *P. jirovecii* infection; the organism can be identified in lavage and in biopsy material by suitable staining.
- Cytomegalovirus infection can be diagnosed by the presence of inclusion bodies in cells normally observed in this infection.
- Fungal infection, particularly *Aspergillus* infection. Aspergilli in the BAL fluid of an immunocompromised patient with "pneumonia" strongly suggests *Aspergillus* infection.
- Opportunistic *cryptococcal* infection and toxoplasmosis may be occasionally diagnosed on a transbronchial biopsy.

If a specific etiology is found by this procedure, the drugs used are, by and large, solely directed toward the eradication of the etiological agent.

Flowchart 1: Management protocol in acutely ill immunocompromised patients with fever and pulmonary infiltrates (see text for role of open lung biopsy and for details of management protocol)



If the patient is too ill for a bronchoalveolar lavage or a transbronchial fiberoptic bronchoscopy, or if the ICU cannot organize these procedures, or if the pathological and microbiological back-up is poor, further management should proceed on an empiric basis. For example, if amoxicillin + clavulinic acid, a third-generation cephalosporin and an aminoglycoside have been used initially with no effect, one could switch to piperacillin-tazobactam plus vancomycin or to a combination of meropenam plus vancomycin. Besides covering Gram-positive and Gram-negative infections, atypical organisms (e.g. *Legionella, Mycoplasma*) should be covered by azithromycin, and fungal infection, if suspected, by amphotericin B. Opportunistic infection may at times be impossibly difficult to diagnose.

In patients with a subacute onset, the possibility of tuberculous pneumonia should always be considered. The diagnosis is generally proven by demonstrating *Tubercle bacilli* in bronchial lavage specimens. Specific treatment consists of rifampicin 600 mg daily, isoniazid 300 mg daily, ethambutol 1 g daily, pyrazinamide 750 mg twice daily and streptomycin 1 g intramuscularly daily.

- If the patient shows diffuse bilateral alveolar, shadowing a third-generation cephalosporin or piperacillin-tazobactam, in combination with an aminoglycoside can be used. This regime may need to be modified depending on the likely Gram-positive or Gram-negative organism responsible for the infection in a given individual. *The sicker the patient, the greater should be the cover for possible invading organisms*. If the X-ray appearances and clinical background are compatible with *Pneumocystis* infection, trimethoprim-sulfamethoxazole combination needs to be given. This is followed by bronchial lavage, brush and transbronchial biopsies for possible diagnostic help. If this is not possible for reasons earlier outlined, or if the diagnostic procedure fails to provide a clue, further treatment remains empiric. Deterioration of the patient, should prompt the use of amphotericin B for *cryptococcal, Aspergillus,* or other rare fungal infections. If Legionnaires' disease is a clinical possibility, erythromycin is added. Disseminated tuberculosis should generally be evident by the demonstration of acid-fast bacilli in the samples obtained through a bronchial lavage.
- If the patient has bilateral pulmonary parahilar interstitial infiltrates, strongly suggestive of *Pneumocystis* infection, a trimethoprim-sulfamethoxazole combination is indicated, and this is followed up with bronchial lavage, bronchial brush biopsy and rarely a transbronchial biopsy, to prove the presence of *P. jirovecii*. If the diagnosis is confirmed, specific treatment is continued for 2 weeks. If unconfirmed, the above-mentioned treatment should still be continued and ganciclovir added for a possible CMV infection.

- The possibility that the shadows or lung infiltrates in the lung could be noninfective in nature should be kept in mind, particularly if investigations for an infective agent are persistently negative and the shadows persist in spite of antibiotic therapy.
- As mentioned in Table 1 earlier, a consideration of the specific nature of the immunocompromised state in a patient and the imaging findings help suggest the possible etiological agents likely to cause pneumonia.

Role of an Open Lung Biopsy

Many units in the West are aggressive in their approach, and perform an open lung biopsy within 24 hours, if the patient deteriorates, to obtain a specific diagnosis of the etiology of the pneumonia. We rarely perform open lung biopsies on our patients, as we feel that most of them are too ill to tolerate the procedure. Thoracoscopic lung biopsies are less traumatic than open lung biopsies. Lung biopsy is recommended under the following circumstances—

- When the patient is not critically ill, when the treatment directed toward the "pneumonia" has not provided definite benefit, and when diagnostic procedures carried out through a fibrotic bronchoscope have provided no yield.
- In subacute or chronic pulmonary infiltrates, the diagnosis of which is undetermined by the procedures mentioned above. The importance of establishing a diagnosis here is that it avoids unnecessary treatment with antibiotics for prolonged periods, this being definitely detrimental for the patient. Subacute or chronic infiltrates may be noninfectious in nature, and a thoracoscopic or an open lung biopsy helps to confirm this. At times, we have diagnosed chronic interstitial pneumonia which does not require any antibiotic treatment on an open lung biopsy. Above all, we have occasionally diagnosed infiltrates to be due to pulmonary tuberculosis, by doing an open lung biopsy in patients, whose clinical features and radiological findings were bizarre, and did not suggest pulmonary tuberculosis in any way.

Important Specific Pulmonary Infections in the Immunocompromised Patients

P. jirovecii pneumonia *P. carinii* (now termed *P. jirovecii*), which was earlier regarded as a protozoal parasite, is now regarded as a fungus; it is an important cause of pneumonia in immunocompromised individuals. It most frequently infects patients with AIDS; in fact, early in the HIV epidemic about 80% of patients with AIDS and pulmonary infiltrates had a PCP.[8] This is because *Pneumocystis* infection is the commonest in patients with severe cell-mediated immune deficiency, and AIDS is an example of the severest form of cellular immunity depression. However, with the widespread use of antiretroviral therapy and chemoprophylaxis against *P. jirovecii*, the incidence has fallen significantly. In an Indian autopsy study on 143 patients with AIDS, only 5% of lung pathologies were caused by *P. jirovecii*.[9] This is because AIDS patients in India, die of pulmonary tuberculosis, before they get a chance to acquire *Pneumocystis* infection (see subsequent Section on Pneumonia in AIDS). *P. jirovecii* is also seen in other diseases with depressed cell-mediated immunity; for example, lymphomas, in children with acute lymphoblastic leukemia, patients on high doses of corticosteroids, organ transplant recipients and allogenic stem-cell transplant patients.

In AIDS, the disease is often subacute or insidious in onset,[10] generally presenting with cough and bilateral perihilar infiltrates which slowly and progressively fan out into the periphery. As the disease progresses, it produces increasing breathlessness, but few physical signs. Hypoxia progressively increases so that the patient finally develops hypoxemic respiratory failure, and at this stage the patient usually gets admitted to an ICU. If the background of AIDS is known, the diagnosis is generally obvious; if AIDS has not been diagnosed, the diagnosis may be missed, if the clinician is unaware of its clinical and radiological features.

In diseases other than AIDS, *P. pneumonia* is more often an acute opportunistic infection, producing fever, increasing breathlessness and progressive interstitial infiltration fanning from the hilum to the periphery, and soon involving the greater part of both lungs. Death results from acute respiratory failure.

In the subacutely ill patients, nebulization of hypertonic saline[11] can give an yield of sputum positive for *P. carinii,* in more than 50–60% of patients. In the acutely ill patients in an intensive care setting, the diagnosis can be proven by bronchial lavage, brush biopsies or transbronchial biopsy as outlined earlier. Open lung biopsies are hardly ever necessary to establish a diagnosis.

Treatment The drug of choice is a trimethoprim-sulfamethoxazole (TMP/SMX) combination, the IV dose being trimethoprim 5 mg/kg and sulfamethoxazole 25 mg/kg given 6 hourly. The oral preparation double strength trimethoprim-sulfamethoxazole (TMP/SMX) in dose of 2 tablets thrice daily is better tolerated than the IV preparation. Adverse reactions are frequent[12] and over 50% of patients treated with this combination exhibit rashes, liver cell, renal dysfunction, leucopenia and thrombocytopenia. A recent study reported that TMP/SMX had an amiloride-like effect, thus partly accounting for the hyponatremia which is frequently associated with the use of these drugs.[13] Clindamycin (300 mg TDS/QDS) plus primaquine (15–30 mg OD) is a reasonable alternative and often one that is better tolerated. Other drugs used include nebulized and IV pentamidine (4 mg/kg IV OD), dapsone (100 mg OD) and atovaquone (750 mg orally thrice daily). Corticosteroids are beneficial as adjunctive therapy in patients with hypoxemic respiratory failure (PaO_2 <65 mm Hg).[14] Methyl prednisolone 40–60 mg administered once to four times a day in tapering doses over 21 days appears beneficial.

The prognosis for the first episode of *P. pneumonia,* if adequately treated, is good. Recovery occurs in 80–90% of patients.[15] Subsequent attacks carry a poorer prognosis.

Acute viral pneumonias requiring critical care The major viral pulmonary infection of concern in immunocompromised patients is the CMV infection. It can occur in any immunocompromised patient, but is particularly common in certain patient populations. It is most common after allogeneic bone marrow transplantation,[16] in organ transplant recipients and in patients with AIDS.

The clinical features are characterized by fever, nonproductive cough and increasing dyspnoea leading to a quickly progressive hypoxemic respiratory failure. A chest X-ray shows progressive interstitial pulmonary infiltrates, often indistinguishable from *P. pneumonia*. A miliary pattern on the chest X-ray is rarely observed in fulminant infections, leading to a quickly evolving arterial hypoxemia and death.

Multisystem involvement is often observed in fulminant infections, and when present, serves in most instances to distinguish CMV from *Pneumocystis* infection. Thus, liver cell dysfunction, leucopenia with atypical peripheral lymphocytes, lymphadenopathy, renal dysfunction probably due to virus-induced glomerulopathy, colitis and ocular changes may be observed. The frequency of CMV infection is undoubtedly underestimated, as diagnosis in critical care settings of developing countries is difficult. An important and rather peculiar feature of CMV infection is the ability of the CMV to further suppress cell-mediated immune responses in the host, thereby predisposing to further opportunistic infections. It is therefore not surprising that in AIDS, CMV infection often co-exists with mycobacterial, and also with *Pneumocystis* infections.[17]

A quick diagnosis of CMV pneumonia in a critically ill patient can be only suspected by the presence of inclusion bodies, within the cytoplasm of host cells in lung tissue obtained through transbronchial or open lung biopsies. A blood examination shows IgM antibodies against the CMV. A polymerase chain reaction (PCR) for CMV DNA is a crucial test; it demonstrates the presence of a significant viral load in CMV infection, even when the IgM antibody is negative.

Cytomegalovirus specific monoclonal antibodies are being studied to allow the diagnosis of CMV pneumonitis in tissues obtained from lung biopsies.

Gancyclovir in a dose of 5 mg/kg 12 hourly for 2–3 weeks is used as treatment. Its main toxic effect is myelosuppression.

Other acute viral pneumonias in immunocompromised patients Several other viral infections can produce acute life-threatening pulmonary infections in immunocompromised patients. Measles and varicella zoster viruses (VZV) may present as disseminated infections with a fulminant fatal pneumonia. Generally, there is no diagnostic difficulty in either case because of the characteristic skin rash in each disease.

Herpes simplex virus (HSV) rarely produces a hemorrhagic tracheobronchitis with a patchy pneumonia. The pathogen in most cases is due to an extension or aspiration of oral herpes simplex lesions, though in some cases, there is a hematogenous spread. Bronchoscopy shows hemorrhagic ulcerating lesions, within the bronchi covered with a white membrane. Material for specific cytological and virological studies may help establish a definite diagnosis. Therapy with IV acyclovir (5 mg/kg, 8 hourly) should be given in these patients. In the West, the incidence of herpes simplex viral infections in immunocompromised patients appears to be on the rise.

Nocardiosis This is an infection produced chiefly by *N. asteroides* in immunocompromised patients. It does not produce respiratory failure but presents in an intensive care setting as a pulmonary shadow of unknown etiology in an immunosuppressed patient admitted for an unrelated problem. The X-ray picture shows one or more shadows often circumscribed and sometimes cavitating. A review of nocardial infection in 160 patients who had undergone heart transplant provides a useful outline of the clinical profile of this disease.[18] Fever and dry cough are presenting features, but as mentioned above, an asymptomatic pulmonary shadow may be the first manifestation in 40% of patients. Though generally subacute in its natural history, in some instances, nocardial pulmonary infection in an immunosuppressed host may resemble an acute bacterial pneumonia.

Nocardial infection can disseminate particularly to the CNS. One or more abscess-like cavities in the lungs and the brain in an immunocompromised patient, should always suggest this diagnosis. Skin lesions occur in the form of nodules, which on biopsy show the presence of *N. asteroides.*

Diagnosis is difficult as *nocardia* is rarely present in sputum samples and cultures are frequently negative. This is one condition where a thoracoscopic or an open lung biopsy is indicated to establish a diagnosis. In two recent patients with nocardiosis, the diagnosis was arrived at by performing a CT-guided biopsy of the lesion in one patient, and by culture of material obtained through bronchial lavage in the other.

Treatment of nocardiosis is with sulfisoxazole (6–12 g/day) for a period of 3–6 months, extending to as long as a year in serious infections. Several authors have suggested that a trimethoprim-sulfamethoxazole combination may be the treatment of choice in nocardial infections.[19] This recommendation is based on a retrospective analysis of a small number of patients. We now use doxycycline 200 mg/day to start with, followed by 100 mg/day for 6 months to a year. Antibiotic sensitivity tests may be of help, if the organism is grown on culture. Anecdotal reports claim success with a number of other drugs, minocycline, cycloserine, erythromycin and ampicillin.

Acute fungal pulmonary infections Fungal infections are being increasingly recognized in immunocompromised patients and invasive fatal pulmonary infections due to *Aspergillus* are probably the commonest of these fungal infections. In AIDS patients however *cryptococcal* lung disease appears to be significantly more common, but rarely leads to respiratory failure. Although disseminated candidiasis is a frequent opportunistic infection in immunocompromised patients in an intensive care setting, isolated or primary

candida pneumonia is rare.[7] Infection caused by the *Mucor* species (mucormycosis) should be kept in mind in immunocompromised patients (particularly in diabetics or those on corticosteroids) who have a maxillary sinusitis, or who have necrotic eschars over the sinuses or within the nasal cavity with orbital swelling and conjunctival edema. *Mucor* tends to invade vessels leading to ischemic necrosis of tissue supplied by these vessels.

Invasive rapidly spreading *Aspergillus* pneumonia almost exclusively occurs in severely immunocompromised and myelosuppressed patients.[7] Severe leucopenia and, in particular, marked granulocytopenia is a major risk factor in the evolution of invasive pulmonary aspergillosis. Patients with acute leukemia develop invasive aspergillosis as a complication 20 times more frequently than patients with lymphomas or recipients of organ transplants.[7] In renal transplant patients, the risk of invasive pulmonary aspergillosis (IPA) increases with the use of high doses of corticosteroids.

Reports from the West continue to stress the importance of acute critical illnesses produced by invasive aspergillosis in patients with neoplastic disease and in heart transplant patients.[7] The spectrum of background diseases predisposing to invasive aspergillosis now includes patients with subacute hepatic necrosis treated with corticosteroids and IV antibiotics.[20] We are fortunate in that the incidence of IPA is low as compared to the West. Perhaps the frequency and the epidemiology of *Aspergillus* infections is governed to an extent by the presence of airborne *Aspergillus* in a particular eco-environment. Outbreaks of this infection have thus been related to the increased presence of this organism in the air, related to construction or to inadequate air conditioning systems.[21-23]

Fever, nonproductive cough, hemoptysis, pleuritic chest pain and a quick deterioration in the general condition of the patient is observed with IPA.

About 10% of immunocompromised patients, may present with a PUO with an X-ray chest which is normal. CT of the chest in these patients may demonstrate nodular infiltrates compatible with IPA.

Invasive pulmonary aspergillosis is sometimes suspected on CT findings in the chest. These include—

- A "halo sign" which is an area of attenuated shadowing surrounding a nodule or an area of consolidation.
- A "crescent sign" which relates to a partially formed cavity due to infarcted lung tissue.

The halo sign is neither very sensitive nor specific, for many molds other than *Aspergillus* (e.g. *fusarium*) may cause a similar pattern on a CT. Radiographic appearances vary from nodular infiltrates to dense consolidation. Because of the angioinvasive nature of the fungus, wedge shaped pleural-based infarct may be observed, which may later cavitate. A CT is mandatory as it reveals lesions not seen on an X-ray chest.

Chronic necrotizing pulmonary aspergillosis (CNPA), producing a critical illness has been reported in insulin dependent diabetics, in patients on a modest dose of corticosteroids, or in patients following radiotherapy to the lungs.

Diagnosis of invasive aspergillosis is difficult. Sputum is rarely present and if present is rarely positive. Sputum cultures take a long time for growth of *Aspergillus* and in critically ill patients, it is wrong to await reports when clinical suspicion is strong. Presence of *Aspergilli* in the BAL fluid in an immunocompromised patient is indicative of Aspergillosis. An HRCT of the chest is far more sensitive in the diagnosis of IPA than an X-ray chest, a sputum examination or a bronchoscopic examination. A transbroncial biopsy is positive for *Aspergillus* in only 50% of patients with invasive disease.[24] An open lung biopsy is diagnostic, but is not performed often, because of the poor condition of the patient. Empiric treatment is both indicated and justified in such situations.

Noninvasive tests include—

- Detection of galactomannan or glucan cell wall antigen on BAL specimen obtained through a fiberoptic bronchoscope or in the blood.
- PCR for *Aspergillus* DNA from the blood. Though highly sensitive, the galactomannan test may give false positive results in patients receiving piperacillin-tazobactam.

Pneumonia in AIDS

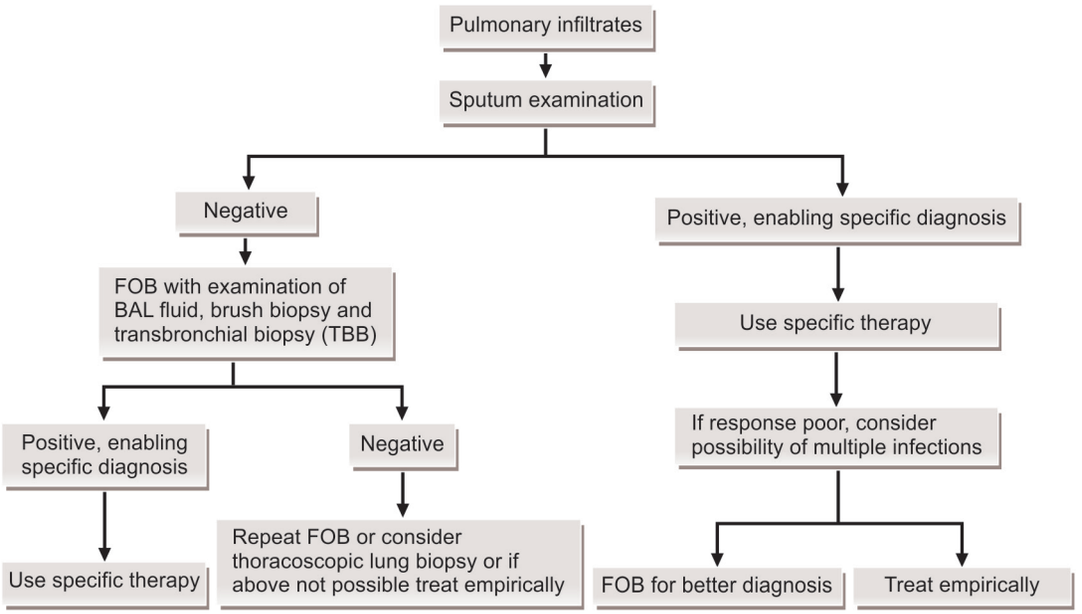
The principles enunciated above in relation to pneumonia in immunosuppressed individuals apply to patients with AIDS as well.

A few points however need to be stressed in relation to these patients—

- There are some differences in the frequency of opportunistic pathogens in this syndrome. Acute disseminated tuberculosis (including lung involvement), is the major opportunistic infection complicating the HIV epidemic worldwide.[25] A study by Selwyn et al. showed a 7.6% incidence of tuberculosis among anergic high-risk HIV-seropositive individuals.[26] It is a general belief that *Pneumocystis* infection is uncommon in India. This is not so; it occurs later than tuberculosis in the natural history of HIV infection. The apparent infrequency of *P. jirovecii* infection in patients with AIDS in India is because these patients are killed by the tubercle bacillus before the CD4 lymphocyte count drops to a level (<200/mm^3) which predisposes them to *P. jirovecii* infection. Also, the latter infection is difficult to prove in units where microbiological and bronchoscopy facilities are inadequate.

  An autopsy study of 143 patients with AIDS from Mumbai in 2001,[9] revealed a pulmonary pathology in 88% of cases. The lesions identified were tuberculosis in 59%, bacterial pneumonias in 18%, CMV infection in 7%, cryptococcal infection in 6%, *Pneumocystis* infection in 5%, aspergillosis in 3%, toxoplasmosis in 1%, Kaposi's sarcoma in 1% and squamous cell carcinoma in 1%. Two or more infections were found in 13%.

Flowchart 2: Algorithm for the diagnostic evaluation of pulmonary infiltrates in patients with AIDS


Pulmonary infiltrates
Sputum examination
Negative
Positive, enabling specific diagnosis
FOB with examination of BAL fluid, brush biopsy and transbronchial biopsy (TBB)
Use specific therapy
If response poor, consider possibility of multiple infections
Positive, enabling specific diagnosis
Negative
Use specific therapy
Repeat FOB or consider thoracoscopic lung biopsy or if above not possible treat empirically
FOB for better diagnosis
Treat empirically

- The clinical features of pulmonary infections in AIDS may be even more subtle than in other immunocompromised patients. This is so with all infections but is particularly observed with *Pneumocystis* infection (which is generally subacute), disseminated tuberculosis and fungal infections.
- Diagnostic procedures like examination of bronchoalveolar lavage fluid or the use of transbronchial biopsy, yield better or more definite results in diagnosing the etiology of acute pulmonary infiltrates in AIDS as compared to other immunocompromised populations.

A plan for diagnostic evaluation of pulmonary infiltrates follows the same principles as in other immunocompromised patients and is briefly illustrated below in Flowchart 2.

Specific antibiotic therapy (with the dose and duration of treatment) for organisms commonly encountered in immunocompromised patients is listed in Table 3.

Disseminated Tuberculosis

This is an extremely important cause of a critical illness demanding intensive care in our country, and probably in all developing countries where tuberculosis is rampant. It occurs chiefly in patients whose cell-mediated immune response is suppressed or compromised. We have observed its frequent occurrence in AIDS, and in patients on chemotherapy or corticosteroids. The combination of chemotherapy and corticosteroids in high doses, given over a prolonged period, is a potent risk factor for hematogenous disseminated tuberculosis.

The clinical features, diagnostic methods, complications and management are described in detail in the Section Fever and Acute Infections in a Critical Care Setting.

Central Nervous System Infections

Immunosuppressed patients have an increased incidence of CNS infections necessitating critical care in an ICU.

Meningitis and brain abscesses are both important complications and their diagnosis should be quick. Meningeal signs are almost never as florid as in patients with a normal immune status. In fact, they may be subtle and it is important to examine the CSF through a lumbar puncture even on a mere suspicion of possible meningitis. If a brain abscess is suspected because of focal signs or because of evidence of increased intracranial pressure, a CT scan of the head with contrast study should be done prior to a spinal tap. Generally, however, in such patients a spinal tap is best avoided particularly if the lesion is subtentorial or there is increased intracranial pressure.

The choice of therapy in pyogenic meningitis depends on the organisms seen on Gram staining of the CSF. Treatment should start promptly, the choice of empiric therapy being based on an evaluation of the clinical background of the individual patient. If the nature of the immunologic defect is known, therapy is easier to plan. For neutropenic patients in whom Gram-negative bacillary infection is a strong possibility, a combination of ceftazidime 2 g intravenously 6 hourly is used. An alternative regime used, as in patients with Gram-negative sepsis, is a combination of meropenem with an aminoglycoside. If a coccal infection is suspected, ampicillin 2 g 4 hourly should be added to the above regime. On the other hand, if these patients have intracranial foreign bodies such as an ommaya reservoir or a shunt, or have undergone a recent neurosurgical procedure, vancomycin 500 mg intravenously 6 hourly should be added.

Table 3: Specific antibiotic therapy for commonly encountered organisms in immunocompromised patients

Organism	*Drug and dose*	*Average duration of treatment*
1. Viruses—		
• Herpes Simplex	Acyclovir 5 mg/kg q8 h IV	7–14 days
	Acyclovir 10 mg/kg IV q8 h (meningitis/encephalitis)	10–14 days
• Herpes Zoster	Acyclovir 10 mg/kg q8 h IV	7–14 days
• CMV	Induction: Ganciclovir 5 mg/kg q12 h IV	14 days (induction)
	Maintenance: Ganciclovir 5 mg/kg (IV) q24 h OR 1 gm (PO) q8 h	3–4 weeks (maintenance)
2. Protozoa—		
• Toxoplasma gondii	Pyrimethamine 200 mg (PO) single dose	
	Followed by 50 mg (<60 kg) to 75 mg (>60 kg)	for 6–8 weeks
	daily orally + sulfadiazine 1 gm q6 h OR	
	Clindamycin 600 mg q6 h PO/IV	
	(up to 1200 mg IV q6 h)	
3. Fungi—		
• Candida species	Caspofungin: 70 mg load then 50 mg daily	Continue till 2 weeks after Blood cultures are negative
	Micafungin 100 mg daily	
	Anidulafungin 200 mg load, then 100 mg daily	
	Liposomal Amphotericin B 3–5 mg/kg daily	
• Aspergillus species	Loading dose: Voriconazole 6 mg/kg IV q12 h	
	Maintenance dose: 4 mg/kg q12 h	
• Cryptococcus neoformans	Induction phase—Amphotericin B deoxycholate 0.7 mg/kg q24 h IV +/- 5-flucytosine 25 mg/kg Orally q6 h	2 weeks
	Consolidation phase: Fluconazole 400 mg (PO) q24 h	8 weeks or until CSF cultures are sterile
	Chronic maintenance therapy: Fluconazole 200 mg (PO)	
	For secondary prophylaxis q24 h	
• P. jirovecii	Trimethoprim 5 mg/kg q6 h IV	21 days
	+ sulfamethoxazole 25 mg/kg q6 h IV	

Note: For Candida species, Fluconazole can be used in less critically ill patients and those who have no recent azole exposure. Fluconazole in such cases is used as loading dose of 800 mg (12 mg/kg), and then 400 mg (6 mg/kg).

Meningitis related to humoral or complement deficiencies is often due to *S. pneumoniae* or *H. influenzae*. Therapeutic regimes should include ceftriaxone 2 g intravenously every 12 hours and vancomycin 30–60 mg/kg 8 hourly. *Listeria monocytogenes* is a rare cause of acute meningitis in patients with cell-mediated immune deficiencies. Therapy for this should include ampicillin 2 g intravenously 4 hourly.

Tuberculous meningitis may occur in immunocompromised patients either by itself, or as a part of disseminated hematogenous disease. The clinical picture may be subacute, or may take the form of a fulminating meningo-encephalitis. Increase in cerebrospinal fluid (CSF) lymphocytes, raised proteins and a lowered CSF sugar level suggest the diagnosis. Acid-fast bacilli are almost never found in the CSF.

Therapy of inflammatory space-occupying lesions must necessarily be empiric before a definitive diagnosis (by an invasive procedure) is made. Pyogenic abscesses are best treated with massive doses of penicillin or ampicillin. Vancomycin should be added to cover a staphylococcal infection. In leucopenic patients, possible Gram-negative infections should be covered by ceftazidime and an aminoglycoside, or piperacillin + tazobactum together with and amikacin.

Tuberculomas and tuberculous abscesses, sometimes multiple, are common in our country and in all third-world countries where the incidence of tuberculosis is high. The CT findings with contrast studies are often distinctive enough to suggest a strong possibility of a tuberculous abscess. Specific treatment includes the use of rifamycin, isoniazid, pyrazinamide,

ethambutol and streptomycin in the doses outlined earlier. Treatment should continue for 9 months to a year.

In patients with a cellular immune defect, a mass lesion may be due to *Toxoplasma* infection. This requires the use of pyrimethamine 25–75 mg orally daily and sulfadiazine 1–2 g orally every 6 hours with leucovorin calcium 10 mg intravenously daily. If toxoplasmosis is proven to be the cause of a mass lesion, all the three drugs mentioned above should be continued for at least 6 weeks, and a maintenance regime with a lower dose of these drugs should be continued life-long in patients with AIDS. Dexamethasone 4 mg 6 hourly intravenously should be used only when mass lesions are associated with cerebral edema and with increased intracranial pressure.

Mass lesions may be due to other disseminated fungal infections. Definitive diagnosis can only be made by invasive procedures like a brain biopsy.

In patients with AIDS, inflammatory mass lesions described above need to be distinguished from tumors, particularly lymphomas, and viral infections, viz. the mass lesions produced by the HSV. The clinical background, the natural history of the disease and the CT findings help in the diagnosis. Definitive diagnosis more often than not, can only be made by a brain biopsy.

Disseminated Presentation

Involvement of two or more organ systems may well be present in infections occurring in immunocompromised patients.

- The lungs and the CNS can both be involved by either *M. tuberculosis*, *Nocardia, Aspergillus* and other mycelia and cryptococcal infections. Pyogenic abscesses can involve both the lung and the brain.
- The lung and mucocutaneous lesions occur with *Aspergillus* and in histoplasmosis (areas endemic to the fungus).
- *Multiple organ systems* Lungs, skin, joints, ocular, liver and spleen involvement can occur with invasive candidiasis. Patients who present with a single organ involvement may after a lapse of time may develop involvement of one or more other organ systems.

INFECTIONS IN PATIENTS WITH AIDS[7]

These patients form a subset of the most severely immunocompromised patients. The principles in relation to infective complications and their management outlined earlier are obviously applicable to these patients as well. The features characterizing pulmonary infiltrates in AIDS have already been briefly dealt with. Sepsis however can originate from almost any other site. The oral cavity, CNS, GI system, urinary system and breached surfaces of skin or mucosa are other important sites of infection in these patients. Great care should be taken to evaluate every possible source of infection; sepsis arising from indwelling catheters or central venous lines assumes special importance.

Fungal esophagitis, fungal (candidal) ulcers involving the lower esophagus and stomach, bleeding from the GI tract, perianal abscesses, perforated diverticulitis or other acute abdominal catastrophes may pose problems in diagnosis and management. Symptoms may be even more insidious than in other subsets of immunocompromised patients. In our country, tuberculosis, *salmonella* infections and overwhelming parasitic infections, head the list of infectious complications in this group of patients. Patients with AIDS form the only group of patients, in our country, in whom disseminated fungal infections (particularly cryptococcal and candidal infections) are quite common. All these infections should be assiduously searched for, investigated and treated. Not uncommonly, fungal, viral and parasitic infections in AIDS may be controlled during the acute stage but cannot be cured. Long-term suppressive therapy is needed to keep them under control, as they often flare up and cause acute illness if suppressive therapy is omitted, or if further deterioration occurs in the immune status of the patient. Infections in AIDS are usually multiple, often recurrent, with multiple organisms involving different sites. They are more severe; more disseminated, and elicit an even poorer tissue and body response as compared to patients immunocompromised due to other causes. They are often characterized by a very high density of organisms, a factor responsible for the poor results of therapy .

Finally, as already stressed earlier, any critical illness in a patient with AIDS may be due to tumors; in our country, lymphomas are probably observed with the same frequency as in the West; Kaposi's sarcoma, however, is comparatively uncommon.

Table 4 gives the list of common opportunistic infections recognized to be associated with HIV infection.

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Table 4: Common opportunistic infections associated with HIV infection

	Clinical manifestations	
Organism	*Common*	*Infrequent*
1. Protozoa—		
• Toxoplasma	Encephalitis, retinochoroiditis	Pneumonia, dissemination
• Cryptosporidium	Enteritis	Cholangitis, bronchopleural lesions
• Isospora belli	Enteritis	
2. Fungi—		
• *P. jirovecii*	Pneumonia	Otitis, dissemination
• Candida spp.	Stomatitis, esophagitis	Proctitis, vaginitis, dissemination
• Cryptococcus neoformans	Meningitis, disseminated disease	Pneumonitis, skin lesions
• Histoplasma	Disseminated disease	
3. Nocardia	Lung abscess	Dissemination
4. Bacteria—		
• M. tuberculosis	Pneumonia, dissemination	Meningitis
• Atypical mycobacteria	Dissemination	Pneumonia, diarrhea
• Salmonella	Diarrhea, sepsis	
• *H. influenzae*	Upper respiratory infection	Pneumonia, sepsis
5. Viruses—		
• Cytomegalovirus	Retino-choroiditis, pneumonia, colitis	Adrenal necrosis, hepatitis, encephalitis, myelitis
• Herpes simplex	Mucocutaneous (mouth, digits, rectum)	Pneumonia, encephalitis
• Herpes zoster	Dermatomal skin lesions	Encephalitis, disseminated skin lesions
• Epstein-Barr	Hairy cell leukoplakia	
6. Helminth—		
• Strongyloides	Hyperinfection syndrome, bronchopneumonia	Dissemination

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SECTION

18

Physical Injuries Requiring Critical Care

- Intensive Care Management of Polytrauma
- Management of Critically Ill Burns Patients
- Critical Care in Poisonings
- Envenomation
- Drowning
- Heat Stroke
- Hypothermia

CHAPTER 64

Intensive Care Management of Polytrauma

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GENERAL CONSIDERATIONS

Polytrauma is a symptom complex with profound patho-metabolic changes.

The incidence of polytrauma is on the rise due to rapid industrialization and urbanization and the need for mechanized transport. Even in rural areas, its impact is seen due to the increased use of motorized equipment.

International data reveals not only an increasing incidence, but also a high early mortality in polytrauma. Violent trauma and road traffic injuries kill more than 2.5 million people in the world every year. According to the World Health Organization, there were 1.6 million violent deaths and 1.2 million deaths from traffic injuries[1,2] for a combined mortality of 48 deaths per 100,000 per year.

Most trauma deaths occur at the scene or in the first hour after trauma. In Western countries, 34–50% of these early deaths occur in hospitals.[3] Many of these deaths are preventable. With adequate prehospital care, with special regard to quick transportation to hospital, maintenance of a patent airway, breathing, circulation by paramedics, the mortality is significantly reduced. However, errors made in the in-hospital period of care are responsible for one-third to two-thirds of the deaths reported by various authors.[3] Of these, intensive care unit errors are reported to be among the most frequent and significant.

India is one of the ten most industrialized nations in the world. While India's vehicle population is less than 5% of the world, it accounts for the highest incidence of accidents in the world. More than 80,000 people lose their lives in accidents every year and it is estimated that about ten times that number are admitted in hospitals with injuries. The analysis from one of the "A" level trauma centers indicates a mortality between 19% and 23%. At the LTMG Hospital, Mumbai, which is one of the leading trauma centers, early intensive care with the participation of multispecialty residents, adequate monitoring, and treatment based on protocols, reduced the mortality of polytrauma from 23% to 16%. Further analysis of the patients salvaged indicated that mortality was highest in those arriving in the hospital after 24 hours and in those with multiple injuries brought to the hospital without adequate care during transportation in the first 6 hours.

These observations indicate that pre-hospital care has a significant role in the management of polytrauma. In most developing countries, pre-hospital care is non-existent. Patients are almost always transferred without any treatment, resulting in asphyxia, hemorrhage and shock.

PATHOPHYSIOLOGY OF TRAUMA VICTIMS

The human body is a superbly balanced mechanism having multiple self-restoring safeguards which are activated when an injury occurs. It is vital to understand the pathophysiology of the human response to trauma, if we wish to reduce the morbidity and mortality of the victim.

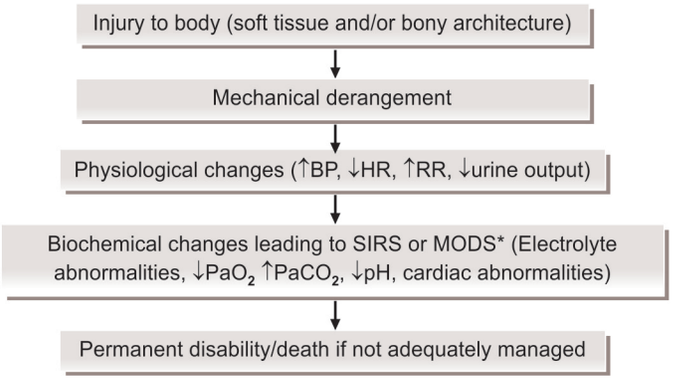
Flowchart 1 summarizes the various changes, and gives an idea of various levels at which one can intervene to interrupt the natural progression leading to death/permanent disability.

Physiological Response of the Body

The "fight or flight" sympathetic response is activated as a result of any trauma. It helps to counter blood loss, alters pulmonary/cardiac functions, and helps maintain viability of vital organs.

Tachycardia, tachypnea, peripheral vasoconstriction and selective shutdown of skeletal muscle microcirculation help

Flowchart 1: Pathophysiology of trauma


Injury to body (soft tissue and/or bony architecture)
Mechanical derangement
Physiological changes (↑BP, ↓HR, ↑RR, ↓urine output)
Biochemical changes leading to SIRS or MODS* (Electrolyte abnormalities, ↓PaO_2 ↑$PaCO_2$, ↓pH, cardiac abnormalities)
Permanent disability/death if not adequately managed

*SIRS—Systemic inflammatory response symdrome
MODS—Multiple organ dysfunction syndrome

in keeping the kidneys, brain and heart adequately supplied with oxygenated blood. The reduced blood supply to skeletal muscle induces anaerobic metabolism and causes metabolic acidosis, which, in turn, stimulates the respiratory centers leading to hyperventilation.

Increased catecholamines, products of the activated complement system, and the liberation of cytokines and other inflammatory mediators by host cells result in widespread damage to the endothelial lining of the microcirculation in various organ systems. There is also probably widespread impairment of cell function in various organs. The end result is multiple organ system failure. Involvement of the lungs is frequent and results in acute lung injury [acute respiratory distress syndrome (ARDS)]. Renal and other systems also show progressive dysfunction. Fat embolism following upon multiple long bones and pelvic fractures can worsen organ dysfunction, with particular reference to the lungs. The presence of an associated head injury or chest injury can depress the respiratory drive, physically impair ventilation and worsen the problems in relation to breathing and gas exchange.

The effect of altered oxygenation, altered acid-base balance and electrolytes can lead to cardiac function abnormalities. Associated chest trauma or direct injury to thoracic viscera results in an added insult to the already stressed circulatory system; this may further lead to hypotension with reduced cerebral and renal perfusion.

Reduced renal perfusion results in electrolyte imbalance; if renal perfusion is significantly low for a prolonged period, it can cause acute tubular necrosis. This situation can develop quite early in an acutely injured person, even though there is no direct renal injury to begin with. Crushing of muscles, development of the compartment syndrome and myonecrosis, severe infection and sepsis are other concomitant causes which can lead to acute renal shutdown. Unless rapid and early precautions are taken in these situations, it is easy to lose an otherwise stable patient.

Presence of major bone fractures causing severe pain, limited mobility and other complications, like fat embolism, injury to vessels or viscera, are important factors which contribute to increased mortality and morbidity.

The overall response of the human body to major stress is catabolic. The effect of this becomes more apparent if the time lag between severe injury and active intervention progressively increases. Absence of prompt critical care in severe trauma results in the human body being trapped in a self-propagating vicious cycle of an increasingly severe systemic inflammatory response, that finally culminates in death. Hence as providers of trauma care, our actions must be *urgent and on all fronts.* This is the precise reason why the patient with polytrauma warrants *intensive trauma care.*

T_1-T_2-T_3 CONCEPT OF TRAUMA CARE

The events from the time of accident to recovery can be chronologically divided into three time spans, denoted as T_1, T_2 and T_3 (Fig. 1).

T_1 is the time of accident which is very short and at the end of which the mechanical damage to the body is complete. Consequently, no further mechanical damage can occur till the point of intervention. The physiological and biological changes are often minimal during this period. A small percentage of patients having injuries incompatible with life (e.g. cerebral lacerations, open or penetrating cardiac injuries, multiple injuries or fractures with severe internal/external bleeding) die during this period. These constitute the *First Peak* of trauma deaths. There is no way of salvaging these patients; the only way to reduce or eliminate this first peak is by preventive safety measures taken in industries or on roads to reduce the incidence of accidents.

T_2 is the period from the point of accident to the point of intervention. This is the time when the patient is literally left to nature for achieving homeostasis. The longer this period, the lesser the chances of a successful outcome. The aim of the *Golden Hour Project,* which was started in cities like Mumbai, was to reduce this T_2 period to a minimum. Intervention within the first 60 minutes of an accident significantly improved the survival rate. A network of co-ordinated ambulances stationed at strategic points and working in unison with the local general practitioners and health workers transported any trauma victim to the hospital within 1 hour of the accident. A central office which regulated the flow of patients to various trauma care centers helped in avoiding bottlenecks in the traffic. Many deaths are thus prevented by the institution of prompt intervention.

T_3 is the intervention-recovery period. The duration of T_3 depends on the efficiency of the trauma care system. Delayed morbidity and mortality can occur in this period.

The most effective overall treatment of trauma victims is only possible if the modular concept of trauma care is adopted (Fig. 2). This includes Types A, B and C level trauma centers, with Type A being the most advanced with specialized units involving neurosurgery, reconstructive surgery, plastic

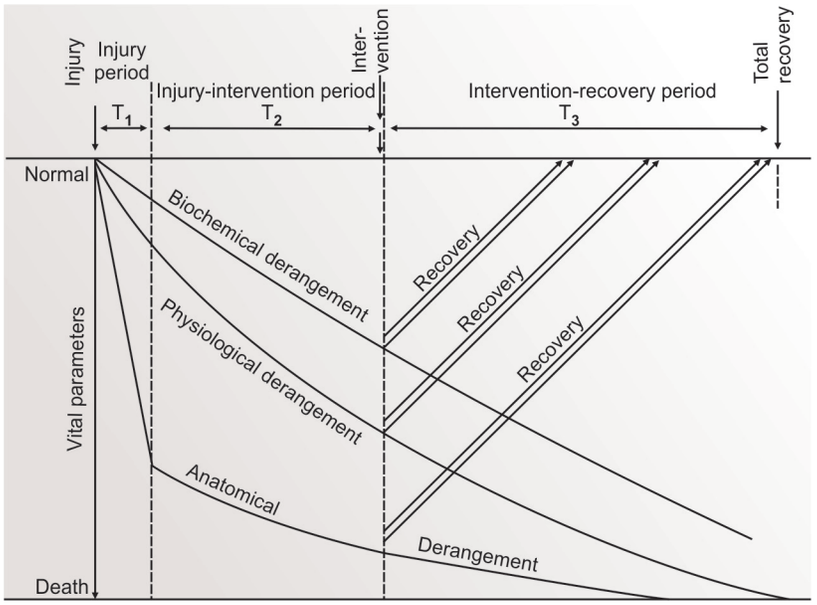


Fig. 1: The injury-intervention-recovery graph (a qualitative representation)

surgery, etc. Type C is the most basic or core unit which can provide the basic trauma intensive care for initial stabilization and emergency primary intervention. After stabilization, the patient can then be shifted to a more advanced unit for specialized treatment and/or rehabilitation.

WHAT CONSTITUTES INTENSIVE TRAUMA CARE

Aim To reduce mortality and long-term morbidity.

Conceptually, it is basically divided into two: (1) pre-hospital care and (2) hospital care.

Pre-hospital Care

The previous concept of 'pick and run' or 'stabilize and transport' has now been replaced by a new concept of evacuation and salvage by paramedics. It essentially consists of: (a) maintaining airway and circulation, (b) stabilizing the neck with a cervical collar, (c) splinting of fractures, (d) transportation of patients on a supine flat board anticipating spinal injury, and (e) covering open wounds with sterile dressings with gentle manual pressure to prevent blood loss and elevating the lower limbs in the presence of shock. The new trauma ambulances are manned by emergency medical officers and emergency technicians whose job is to initiate resuscitation and maintain the patient's basic life support, as also to communicate during transportation with hospital care units. These paramedics assess the severity of injury and transport patients to a specific center for initial and further management. This concept reduces the initiation time of T_2 concept as also the load on A-level trauma centers. It also helps to transport patients to appropriate centers.

Intensive Care Management[4,5]

The first 60 minutes are the "Golden Hour" for trauma victims.

Primary Survey

The primary survey is remembered as the A B C D E of trauma. Primary assessment of injury and resuscitation should be carried out simultaneously.

Airway

It is vital to look out for any obstruction to the airway. This could result from foreign bodies, facial fractures, bleeding or secretions. Snoring or gurgling sounds indicate an upper airway obstruction due to falling back of the tongue, or blood or vomitus in the oral cavity. At times, the patency of the airway may be compromised because of head injury or intoxication (notably alcohol or narcotics). The mouth should be cleared of all debris and an oropharyngeal airway inserted. A patient who verbalizes without stridor or hoarseness usually has a patent airway. It is however important to realize that airway compromise can come on later. This should be promptly recognized and the airway properly secured as an immediate intervention.

In many trauma patients, the airway can only be secured by endotracheal intubation with a cuffed endotracheal tube. It not only keeps the airway patent, but also guards the tracheobronchial tree from aspiration of blood or vomitus in unconscious patients. *One should always bear in mind the possibility of a cervical spine fracture, and the neck should therefore be kept in the neutral position to avoid injury to the spinal cord during intubation.* A nasotracheal intubation may be necessary in these patients. Rarely a tracheostomy may be necessary, particularly in patients with faciomaxillary injuries or fracture of the cervical spine.

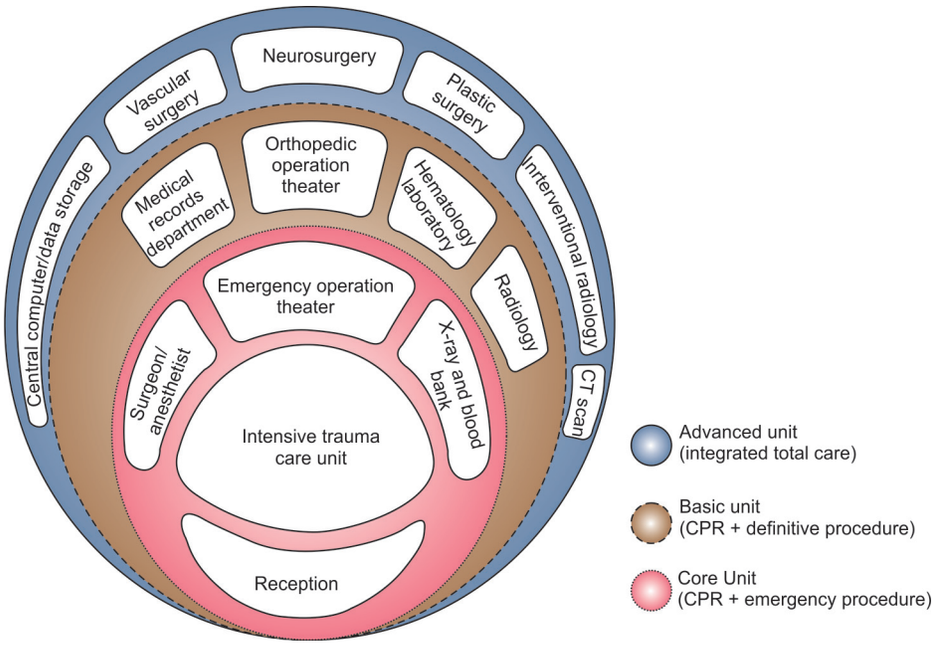


Fig. 2: Modular system of trauma units

Trauma victims may have a laryngeal, tracheal or bronchial disruption. This usually follows crush injuries and is to be suspected in the presence of hemoptysis, surgical emphysema and pneumothorax. Urgent surgical repair becomes necessary to allow preservation of airway integrity.

Breathing and Ventilation

A quick but careful clinical examination helps. Diminished chest excursions may be due to: intracranial injury, pain related to fractured ribs, or a pneumothorax or hemothorax. A massive atelectasis of the lung may produce similar physical signs. Diminished or absent breath sounds on either side might be related to hemothorax, pneumothorax, massive atelectasis or pulmonary contusion. Deviation of the trachea to the opposite side is seen with a pneumothorax, hemothorax or to a large hematoma in the neck. A careful look for obvious fracture of ribs and the presence of a flail chest is important. There are two important points to note while assessing breathing and ventilation—

1. It may be difficult to distinguish airway compromise from ventilatory failure in some patients.
2. A patient presenting with dyspnea may have several causes for it. Massive pulmonary contusions are one of the important causes.

High flow oxygen is used for all patients. If breathing and ventilation are seen to be jeopardized, bag mask ventilation using 100% oxygen should be promptly started to achieve good oxygenation. If for whatever reason ventilation is unsatisfactory, intubation with mechanical ventilatory support should be given. It should be kept in mind that positive pressure ventilation would worsen a pneumothorax if that is present. A pneumothorax and/or a hemothorax need to be promptly drained to allow effective ventilation. It is important to achieve an O_2 saturation of well over 90%.

Circulation and Control of Hemorrhage

Blood volume and cardiac output The clinical features of blood loss and poor perfusion are easily recognized. A fast thready pulse, hypotension, pale ashen skin, poor capillary refill, sweating, increasing mental obtundation, and little or no urinary output are the classic features of hemorrhagic shock.

Bleeding External bleeding is obvious and should be stopped by pressure or by ligation of the bleeding vessel, if possible. Occult bleeding should always be suspected if there are signs of shock without external blood loss. Common sites of internal bleeding are—

- *Intra-abdominal* This may be present without any evidence of laceration or external injury. Injuries to the liver, laceration or rupture of the spleen, large retroperitoneal hematomas should be kept in mind. Distension of the abdomen and generalized or localized tenderness should be looked out for. An ultrasound-guided abdominal paracentesis may confirm the presence of blood in the peritoneal cavity. A four-quadrant abdominal paracentesis is often adviced when there is a strong suspicion of an intra-abdominal bleed.
- *Chest* The presence of rib fractures dullness on percussion and diminished breath sounds lend suspicion to the presence of pleural effusion. A chest X-ray can confirm fluid within the pleural space.
- *Fractures of the pelvic and/or long bones such as the femur* A fracture of the femur can lead to loss of as much as one or two units of blood within the tissues and muscles of the thigh.

Points to remember with regard to circulatory shock from blood loss and hypovolemia are listed as follows—

- Elderly patients decompensate rapidly; marked tachycardia may be absent. Young patients have more reserve and may not show signs of shock unless markedly volume depleted.
- Patients on β-blockers may not show tachycardia.
- Internal bleeding may be present from *multiple sites* in trauma victims who are in shock due to blood loss.
- Important complications following trauma producing severe shock and mimicking hemorrhagic shock are tension pneumothorax and cardiac tamponade. These complications may also well exist side-by-side with hemorrhagic shock. Finally, severe contusions of the heart can effectively reduce cardiac function and output resulting in the picture of cardiogenic shock.

Circulatory shock should be managed on a war footing. Two large bore intravenous lines should be inserted in two peripheral veins one above and the other below the diaphragm to allow volume replacement. If a peripheral vein is inaccessible, a large single lumen catheter is inserted into a central vein through which fluid is administered. One to two liters of Ringer's lactate solution are administered promptly, and this usually restores the normal pulse and blood pressure if the blood loss is less than 15% and there is no persistent bleeding. If 2 L of Ringer's lactate solution fail to restore blood volume and the patient remains hemodynamically unstable, 2 more liters are infused and blood transfusions are also given. If hypotension persists despite infusion of 4 L of Ringer's lactate, colloids and blood, the blood loss is likely to be greater than 40%. If the patient needs surgery, resuscitation is continued in the operation theater.

Efficacy of volume replacement is gauged chiefly on clinical grounds—significant improvement in pulse rate, blood pressure, skin color, capillary refill, mental state and urine output. Metabolic acidosis is corrected following volume resuscitation and the blood lactate levels return to normal or near normal.

Disability or Neurological Status

A rapid neurological examination is important. The following features should be carefully looked out for—

- Glasgow Coma Score (3–15)—
  - Eye opening 1–4.
  - Motor response 1–6.
  - Verbal response 1–5.
- Pupillary size and reactivity.
- Presence of lateralizing signs.
- Presence of possible spinal injury and, if so, at what level.

It is important to note that a lucid interval may be present before an intracranial lesion manifests itself clinically.

Exposure/Environmental Control

It is important to remove all clothing to allow a full examination and a thorough inspection of injuries. After this has been done, the patient should be well covered; hypothermia should be avoided and, if present, countered by a warmer blanket. Hypothermia worsens bleeding and outcomes in trauma.

Adjuncts to the Primary Survey

Certain interventions and procedures are necessary during the evaluation and resuscitation of the trauma patient. These are performed during the primary survey or immediately after. These include—

- *Continuous electrocardiography (ECG) monitoring* A full ECG is done to start with and subsequently if there is any arrhythmia or ST segment changes.
- *Pulse oximetry* The O_2 saturation is kept greater than 90%.
- Insertion of a urinary catheter to assess urine output. It is important to assess for urethral injury by noting any bruising of the perineum or bleeding through the urethral meatus before attempting to insert a catheter.
- *Insertion of a nasogastric tube* Stomach contents should be aspirated to prevent risk of aspiration pneumonia.
- Arterial line for continuous blood pressure monitoring.
- Urgent X-ray of the chest, pelvic films, if there is a blunt trauma or a penetrating wound to the abdomen. Other imaging studies are done as determined by the clinical situation and the nature of the trauma. An X-ray of the cervical spine is important.

Secondary Survey

After a primary survey is complete and resuscitation started, a very careful secondary survey is carried out with detailed, careful examination of all different body areas.

It is important to ask from relatives or friends any history of drug allergy, any medication the trauma victim has been taking, a history of past illness and the time of the last meal before trauma. Details of the nature of trauma or accident should also be elicited.

Clinical examination of different areas should start with the head and systemically proceed downwards.

Head

Head should be carefully examined for lacerations, hematomas, eye injuries and vision.

Maxillofacial Area

Maxillofacial injuries should be carefully looked for facial nerve injuries and intraoral mandible fracture, in particular.

Neck

The neck should be examined for crepitus, hematomas, tracheal shift and tenderness over the cervical spine. The venous pressure should be assessed clinically.

Chest and Heart

A careful examination of the chest should be performed. Evidence for fracture of ribs and sternum, lacerations

over the chest and the presence of crepitus should be sought. Abnormalities in chest expansion, percussion and auscultatory findings should be noted. A special look for the presence of pericardial effusion or cardiac tamponade is necessary. The heart should be carefully auscultated for a gallop. Crepitations over the lungs signify retained secretions or pulmonary edema. A noteworthy cause of pulmonary edema is left ventricular failure following upon contusion of the heart. An echocardiogram will help gauge systolic and diastolic cardiac function.

Arrhythmias need prompt treatment. The occurrence of ventricular tachycardia causing hemodynamic instability or ventricular fibrilation at any point in time will require DC defibrilation, starting with a DC shock of 200 J, and increasing, if necessary, to 300 J. Cardiopulmonary resuscitation is unquestionably of prime importance and of immediate priority in trauma patients who require it (for details see Chapter Cardiopulmonary Resuscitation and Cerebral Preservation in Adults).

Abdomen

One should look for evidence of bruising, laceration, distension, tenderness, discoloration, suggesting underlying hematoma, and for the presence or absence of bowel sounds. A USG of the abdomen may provide valuable information.

Perineum

A search should be made for hematomas, tenderness on palpation, vaginal tears, rectal bleeding and bleeding from the urethral meatus.

Limbs

Examiner should look out for deformity, crepitus on movement, distal pulses, hematomas and any possible injury to nerves and vessels.

Central Nervous System

A detailed neurological examination should be performed to determine if there are lateralizing signs or if there is evidence to suggest injury to the brainstem. In spinal cord injuries, the level of the lesion should be determined, if possible, on clinical examination.

Tertiary Survey

It is crucial for intensivists in the ICU to perform a continual reassessment as outlined in the secondary survey. The response to resuscitation measures is carefully assessed, and complications arising subsequently promptly identified and treated.

Major complications to be watched out for and appropriately treated are infections related to trauma, nosocomial infections, pneumonia, sepsis, ARDS, renal dysfunction and the multiple organ dysfunction syndrome. Metabolic disturbances include fluid and electrolyte disturbances as also acid-base disturbances.

MAJOR IMMEDIATE LIFE-THREATENING COMPLICATIONS

Cardiac Tamponade

Cardiac tamponade is generally observed after blunt injury or crush injuries to the chest, in patients with a fracture of the sternum, fracture of the ribs and in patients with a flail chest. Any intrathoracic injury in a trauma patient should prompt the intensivist to look out for a possible cardiac tamponade.

Cardiac tamponade is typically characterized by tachycardia, an increase in central venous pressure, hypotension and the clinical features of shock. The central venous pressure is however not always sufficiently raised and may even be normal if there is associated hypovolemia. Echocardiography helps in the diagnosis. An X-ray of the chest may show an enlarged cardiac silhouette with a widened mediastinum.

Pericardiocentesis relieves the tamponade; this may have to be repeated. Surgical drainage through a pericardial window is the treatment of choice (see Critical Care in Relation to Cardiovascular System).

Tension Pneumothorax

This is a frequent life-threatening emergency in trauma patients. It should always be looked for. The presentation is with breathlessness, respiratory distress, absent breath sounds over the affected side, shift of the mediastinum to the opposite side and features of shock—tachycardia, hypotension and hypoxia. In a dire emergency, a needle decompression (through the second intercostal space in the midclavicular line) of the pneumothorax should be done. A chest tube drain connected to an underwater seal can then follow.

Massive Hemothorax

Massive hemothorax presents as hemorrhagic shock. A dull percussion note over the hemothorax with diminished or absent breath sounds is noticed. An X-ray chest shows massive intrapleural opacity. A CT chest (if the patient is stable) confirms the diagnosis.

Resuscitation with fluid and blood replacement, together with chest tube drainage, is promptly done. Surgery is often needed to identify and stop the source of bleed.

Contusion of the Heart

A severe contusion of the heart leads to hypotension, and tachycardia despite adequate fluid replacement. Arrhythmias may be the presenting feature. It should be noted that the estimation of cardiac enzymes (creatinine phosphokinase and troponin) has no proven value in the diagnosis of cardiac contusion following blunt injury. Echocardiography shows impaired wall motion over the area of contusion. ECG shows ST-T changes which may be indistinguishable from those seen in myocardial infarction. Treatment is largely supportive, chiefly with the use of inotropic drugs.

Flail Chest

A flail chest is obvious on clinical examination. If not promptly treated, it leads to progressive hypoxia or to hypoxic and hypercapnic respiratory failure, to atelectasis of segments or even a lobe and retained secretions within the chest.

An X-ray of the chest and, if possible, a CT of the chest allows a detailed evaluation of the injuries to ribs and/or sternum.

Treatment consists of adequate pain relief, bronchial toilet and endotracheal intubation with ventilator support till the chest stabilizes. Non-invasive ventilator support often suffices if the degree of injury is not marked.

Injuries to the Liver, Spleen, Gut and Pelvis

Injuries to the liver, spleen lead to profuse intra-abdominal hemorrhage causing hemorrhagic shock and abdominal distension. A peritoneal aspirate draws frank blood. Injury to the pelvis and pelvic bones produces a similar picture. A laparotomy with removal of the spleen if there is a rupture or severe laceration, and careful surgical attention to a lacerated liver are life-saving. It is important to stabilize the pelvis in the presence of pelvic fractures to reduce venous oozing. Perforation or a tear in the gut is a cause for distension, with signs of peritonitis.

Head Injury

This has been dealt with in the Chapter "Neurological Problems".

Cervical Cord Injury[6]

It is vital to exclude cervical cord injury in a traumatic victim. Till such time as this is determined, the head is kept in a neutral position. Neurosurgical advice and the advice of a spinal surgeon should be taken promptly for diagnosis and management.

ROLE OF MECHANICAL VENTILATION IN TRAUMA PATIENTS

Indications[2]

Ventilator support is mandatory for patients with head injury, chest injury (flail chest with pulmonary contusion), high cervical cord injury, acute lung injury (ARDS), sepsis syndrome and severe pneumonia. Elective mechanical ventilation is also indicated: (i) in patients with blood loss greater than 40% of estimated blood volume, hematocrit less than 30% and hemodynamic instability (low blood pressure, tachycardia, reduced urine output and other features of shock); (ii) in patients with an injury severity score greater than 30; (iii) in patients with multiple fractures (polytrauma); and (iv) in some patients with head injury to control intracranial pressure, and thereby reduce mortality and morbidity.

Ventilator support should not be delayed till a point in time when the patient is in severe respiratory distress or is obviously cyanosed. The indications for initiating ventilatory support are based on clinical assessment and results of arterial blood gases. Indications, together with details on management of ventilatory support, have been dealt with in the Chapter Mechanical Ventilation in the Critically Ill.

Weaning from Mechanical Ventilation[3]

Every effort should be made to discontinue ventilatory support as soon as the patient is hemodynamically stable and is able to resume and sustain spontaneous ventilation. Weaning criteria have been discussed in the Chapter Mechanical Ventilation in the Critically Ill.

RE-EVALUATION AND CONTINUOUS RE-ASSESSMENT

Re-evaluation and re-assessment is vital all through the patient's stay in the ICU. It enables the intensivist to detect complications—as, for example, renewed bleeding, complicating infection, sepsis and ARDS. At times, re-surgery or reconstructive procedures are necessary within 48–72 hours of the primary treatment. Delayed deaths or complications due to lack of adequate or infrequent follow-up will lead to loss of human life, and will negate the effort and expenditure spent on initial pick-up and stabilization.

APPROACH TO SKELETAL INJURIES IN POLYTRAUMA PATIENTS

Multiple fractures are often observed in polytrauma patients and, at times, may dominate the clinical picture. The timing of surgical interference with regard to skeletal injuries as also the nature and extent of surgery that should be performed have been subjects of continuing discussion. Current opinion on this subject is embodied in the concept of damage control; this concept plays an important role in the early care of polytrauma patients with severe skeletal injury. The patients are essentially categorized into four groups—

1. Stable patients after initial resuscitation, stabilized visceral injury with maintenance of basic parameters.
2. Borderline patients, well resuscitated after major chest or abdominal injury and major skeletal fractures.
3. Unstable patients with major skeletal injury and visceral injury after initial management.
4. Severely ill polytraumatized patients who are extremely unstable.

"Damage control" concept indicates the following approach. In groups I and II, early skeletal fixation can be advocated. The operation should be done as early as possible, and the preference is for minimally invasive surgery, e.g. use of external skeletal stabilization in injury to the pelvis and closed intramedullary nailing using unreamed

nails in proximal fractures. However, in Groups III and IV, the damage control operation concept envisages a stagewise approach.

Stage I. Management in the emergency room and lifesaving operations like exploration of visceral injury to control hemorrhage and external skeletal stabilization of pelvic or proximal fractures.

Stage II. Shift to ICU for intensive monitoring and further stabilization till the metabolic response to trauma is assessed and the patient's parameters return to normal, indicating a reduction in the proinflammatory response. Urgent surgery is required for head and brain injuries, for fractures with severe soft tissue injuries, visceral injuries and spinal cord injuries.

Stage III. Definitive reconstruction of the chest or abdominal trauma or definitive osteosynthesis using plate, intramedullary nail or screws is usually carried out between 7 and 10 days.

The incidence of infection following temporary external skeletal fixation, with conversion to internal fixation within 1–2 weeks is the same as that observed with primary intramedullary nailing.[7] Damage control orthopedic surgery has helped in early total stabilization of the patient, reduction in the need for ventilatory support, better pain relief and prevention of ARDS. Pain relief following definitive skeletal stabilization and very early mobilization of the injured limb or limbs reduce the chances of postimmobilization muscle atrophy and helps the patient attain a positive nitrogen balance. There is also a dramatic improvement in the functional and psychosomatic state of the patient. The advent of minimally invasive surgery and new implants has dramatically reduced the duration of hospital stay, has enabled early ambulation and has resulted in a reduction in secondary complications.

Prevention of Infection

Trauma patients have a reduced capacity to fight infections, as the immune system is depressed under these conditions. The body is in a catabolic state following injury and subsequent surgical intervention. The use of steroids further reduces the capacity of the body to fight infection. Blood transfusions, presence of intravenous lines, central line catheters, urinary catheters, and endotracheal or tracheostomy tubes are all potential sources of sepsis.

The bedridden patient is also more prone to develop bedsores and basal hypostatic pneumonia. These factors all predispose to the development of overt or occult infection in polytrauma patients. Open fractures and compound injuries further aggravate the problem. If infection occurs in these critically ill patients, it can rapidly push them downhill; prophylactic antibiotics are thus preferable. They should cover both Gram-positive as well as Gram-negative organisms, and also anaerobes. A combination of ampicillin with an aminoglycoside and metronidazole is usually used. Use of more specific antibiotics after culture and specific testing for antibiotic sensitivity is preferable, and can be instituted at a later date. If a specific infection is identified (e.g. urinary tract infection or bone infection), a more specific antibiotic having better penetration in these systems can be used. General aseptic measures and limiting of traffic in the intensive care trauma unit will help in reducing the incidence of these infections. Early mobilization of the patient by fixing bony injuries surgically will go a long way in improving the general condition of the patient, and will thereby reduce the incidence of deep vein thrombosis, basal atelectasis, pneumonia and bed sores.

Nutritional Support

It cannot be overstressed that good nutrition is essential for survival in severe trauma victims. The importance of this is sadly ignored in many units in our country, resulting in a high morbidity and mortality. Enteral feeding is the best way of ensuring proper nutrition to a patient. However many situations preclude the use of the enteral route, and force the physician to resort to the parenteral route (see Chapter Nutritional Support in the Critically Ill Adult).

Pain Relief in the Trauma Victim[8]

This is an important feature in the care of critically ill trauma patients. Various methods are used for pain relief, which are as follows—

- Patient-controlled analgesia.[9] A pump containing a maximally allowed total dose of an analgesic (usually narcotics like morphine or pethidine) is set up. The patient has a push button which when pressed will inject a small amount of the drug intravenously. A lag time is adjusted between two successive injections to prevent a patient from overdosing himself by repeated use of the device. This is a very good system as the patient can himself decide when he requires relief from pain.[8,10]
- Continuous analgesic intravenous infusion of small doses of morphine (0.1 mg/minute) provides effective pain relief in most cases. Alternatively, 30 mg pentazocine together with 50 mg pethidine is added to 500 mL of 5% dextrose/N saline and given intravenously as a slow infusion over 5–6 hours. This drip can be repeated after 12 hours depending on the patient's needs.
- Oral analgesics can be given if the patient can tolerate them.
- Regional blocks to anesthetize the painful area (e.g. intercostal blocks in rib fractures where breathing is impaired due to pain) are also used to relieve pain.
- The placement of an epidural catheter with continuous patient-controlled/physician-controlled epidural injections of appropriate analgesics is being increasingly used in the ICU. In our set-up, we commonly use buprenorphine 150 μg, diluted in 10–20 mL of normal saline administered slowly. This provides highly effective pain relief, the analgesic effect lasting for approximately

12–16 hours. Morphine or pethidine may also be used via the epidural route. In acute cases, pain relief should consist of a combination of analgesics. Non-narcotics like diclofenac sodium can be combined with narcotics like morphine, pethidine or their derivatives. In cases of head injury, where the level of consciousness needs to be assessed, narcotic analgesics should be avoided. Effective pain relief reduces the patient's anxiety and helps in controlling excessive sympathetic outflow.

Splinting of fractures, use of pinless fixators to stabilize broken limbs and subsequent early stabilization, all go a long way in effective pain relief.[8,10]

General Nursing Care and Physiotherapy

Specific care to prevent bedsores is necessary in debilitated patients. Special foam mattresses, alternately inflating-deflating air beds and waterbeds are various ways of solving dependent skin pressure problems. Log rolling of the patient, active movements and keeping the dependent pressure-bearing skin points dry are also important. Deep breathing exercises and chest physiotherapy are essential in most patients. Passive mobilization of all joints, splinting of joints in their functional position in order to prevent contractures and active movements to prevent muscle wasting are also necessary. Care of the eyes and mouth (especially in unconscious patients) also constitutes an important aspect of general nursing in a severely traumatized victim.

Long-term Rehabilitation

This should be planned and discussed with the patient, keeping in mind his realistic functional outcome as soon as possible. This will allow the patient to mentally accept his disability, and will give him a psychological boost to try for maximum possible recovery.

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CHAPTER 65

Management of Critically Ill Burns Patients

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GENERAL CONSIDERATIONS

It is now universally accepted that burns are essentially a medical problem, at least in the initial stages. The alterations in circulatory hemodynamics, renal function, cardiorespiratory physiology, the gastrointestinal (GI) and the hematopoietic systems, all require the attention of a team of specialists. Thus a team approach is required for the management of major burns.

In India, burns are the second most common cause of injury after road accidents. Women and children are involved in 80% of burn accidents; the majority of women who get burnt are between the ages of 15 and 20 years. Around 75% of burns occur at home.[1] Burn accidents occur throughout the year, but are commoner during the cold season. This is largely because the cold season is generally windy; it is the wind which fans a fire causing more extensive burns. During the festive season of Diwali (the festival of lights), when firecrackers are widely used, burn accidents tend to increase in number. Suicidal and homicidal burns account for approximately 5% of all burn accidents, particularly in young women. The majority of burns occur in the homes of the poor, which usually are small and at ground level. Here it is easy for the victim to rush out and seek help, and respiratory injury is uncommon. The loosely wrapped *saree* is ideal for burning; the thighs and legs which are the best skin donor areas get damaged in *saree* burns. It is an often repeated myth that the Indian burns patient is anemic and hypoproteinemic. They become so after the burns due to inadequate management.

Burns involving 70–80% of body surface area have a 100% mortality. In good burns centers, the mortality rate is now less than 50%.[2] There have been two major advances responsible for the sharp reduction in the mortality of severe burns—

- The first is the quick removal of burnt tissue prior to the onset of infection, and covering of the wound with available autoskin grafts and skin substitutes. Unfortunately, in poor developing countries like India, facilities and infrastructure for prompt surgery in severe burns exist only in very few centers. Mortality in extensive burns thus continues to be forbiddingly high.
- The second is the improvement in the critical care of burns patients, which enables the prevention of multiple organ failure during the period of resuscitation, surgical excision of the burns, and the healing process.[2]

The occurence of multiple organ failure carries a forbiddingly high mortality (>80-90%) and its treatment in the presence of burnt tissue is impossibly difficult, chiefly because the presence of remaining burnt tissue perpetuates and worsens organ system dysfunction. Although the critical care of burns patients has improved in the large centers of India, much more needs to be done in the country for better care. The leading cause of death from burns in poor countries is still sepsis and its complications, whereas in the West, the leading cause of death is now respiratory failure.

PATHOPHYSIOLOGY OF THE BURN WOUND

Skin is damaged by the total quantity of heat applied to it, i.e. the intensity of the heat and the duration of time the heat is in contact with the tissue.

Jackson described three concentric zones of burn injury.[3,4] These zones are illustrated in Figure 1.

The central "Zone of Coagulation" represents the area of maximum damage, and consists of protein coagulation of the tissues including the blood vessels. Blood flow through the affected arterial and venous channels ceases, resulting in a state of irreversible tissue death.

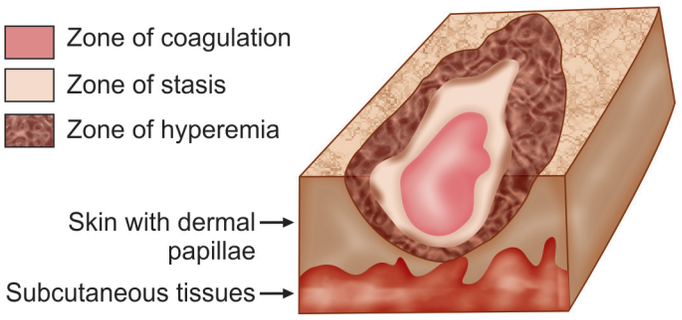
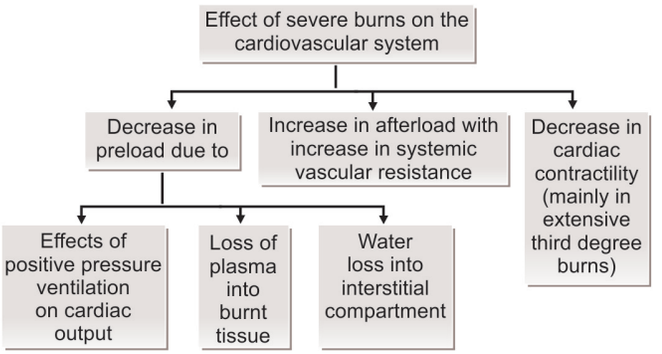


Fig. 1: The three concentric zones of burn injury as described by Jackson
Source: Zawacki BE. Reversal of capillary stasis and prevention of necrosis in burns. Ann Surg. 1974;180(1):98-102.

Flowchart 1: Cardiovascular response to severe burn injury


Effect of severe burns on the cardiovascular system
Decrease in preload due to
Increase in afterload with increase in systemic vascular resistance
Decrease in cardiac contractility (mainly in extensive third degree burns)
Effects of positive pressure ventilation on cardiac output
Loss of plasma into burnt tissue
Water loss into interstitial compartment

This central zone is surrounded by a zone of less damaged tissue, known as the "Zone of Stasis". The blood flow through this zone is completely slowed down, and tissues are starved of oxygen and nutrients. If left unprotected as with exposure treatment, this zone becomes dried up, desiccated, infected and the cells become irreversibly dead. If managed properly, the damage may be reversed and the "Zone of Stasis" comes back to life. The aim of modern burns management is to prevent this "Zone of Stasis" from getting dried up or infected. This can be achieved by the application of autografts, homografts, xenografts (other animal skin), synthetic skins, cultured skins or potato peel bandages.[5] The burn wound must be kept moist, and should not become infected. Wound healing must not be disturbed by traumatic dressings.

Surrounding both these zones is the zone of least damage, the "Zone of Hyperemia". In this zone, the cells are hyperemic, and heal spontaneously if provided with adequate care.

SYSTEMIC RESPONSE TO BURN INJURY[6]

Cardiovascular System

The initial response to burn injury is decreased cardiac output and increased systemic vascular resistance (Flowchart 1). This is proportionate to the size of the burn and the severity of hypovolemia that may be allowed to occur. If corrected rapidly, the process may be reversed, the cardiac output increases and the peripheral vascular resistance decreases. During the second 24 hours post-burn period, the post-burn capillary hyperpermeability decreases, the extravasated fluid from the interstitial compartment returns to the vascular compartment, the volume deficit is corrected, and the cardiac output increases to above normal levels. It has been shown that the increase in blood flow is more in the burnt tissue than elsewhere, thus optimizing wound healing.

Respiratory System

Pulmonary complications are an important cause of morbidity and mortality, particularly in the West. Thermal injury in a closed environment causes pulmonary inhalation injury that can seriously damage the upper airways, larynx, trachea, bronchial tree and the pulmonary parenchyma. In addition, intoxication can result from inhalation of combustion products; the most important of these are carbon monoxide (CO) and cyanide. The physiopathology of pulmonary changes in severe burns is due to many factors. These include thermal inhalation injury, chemical irritation by smoke and other chemicals, secondary infection, the occurrence of acute lung injury (ARDS), fluid overloading and pulmonary embolism.

Physiological changes occur in the respiratory tract after every major burn injury. The respiratory rate and tidal volume increase in direct proportion to the size of the burn. With the large volume of resuscitation fluids infused, the chest wall edema increases considerably, and if treated by exposure, any burn on the thorax forms a tough constrictive eschar, which restricts movements of the thoracic cage. This requires correction with urgent escharotomy. However, it may be mentioned at this stage that the use of potato peel bandages keeps the burn wound supple, and has obviated the need for escharotomy in any patient, except when the patient reaches the burn center late with already established, constricting eschars.

By the 3rd to 5th day post-burn, the extravascular fluid gets reabsorbed, and if the patient has been overinfused, pulmonary edema progressing to acute lung injury (ARDS) may result. Hence, infusion of fluids during the initial resuscitation period has to be carefully calculated so as to maintain a normal blood volume, as also adequate tissue perfusion and renal perfusion.

Arterial hypoxia (a fall in PaO_2) may occur at the very start in severe burns. In other cases, arterial hypoxemia and hypercapnia become manifest 8–14 days following the burns. Ventilation-perfusion inequalities, increase in the right to left shunt within the lungs, and inadequate ventilation in relation to metabolic needs are responsible for these blood gas changes.

Renal System

With the onset of hypovolemia following burns, the renal blood flow and glomerular filtration rate are both considerably reduced. If not corrected early, this may result in acute tubular necrosis and renal shutdown. Early and adequate correction of hypovolemia is hence essential in the treatment

of burns. Forty-eight hours following burns, when resorption of the extravasated fluid takes place, diuresis occurs.

Gastrointestinal System

Acute ulceration of the stomach or duodenum (Curling's ulcer) occurs in about 11% of burns population. Multiple acute erosions may also occur and can cause severe GI bleeds. Post-burn hypovolemia is also accompanied by reduction of GI tract blood flow which manifests as ileus. If hypovolemia is not allowed to supervene, this is rapidly corrected and ileus does not occur. Ileus causes gastric and intestinal distension and stasis with an increasing likelihood of translocation of intestinal bacteria. Contrary to earlier practice, early post-burn feeding is now encouraged not only to provide nutrition through the natural pathway but also to preserve the integrity of the gut and to offset the complications which may ensue from bacterial translocation.

Central Nervous System

Specific neurologic changes following burn injury have not been described. Restlessness, disorientation and fits are observed and indicate cerebral hypoxia, cerebral edema, fluid and electrolyte imbalance or sepsis. These should be investigated and corrected early.

Hematopoietic System

The red cells circulating in the burnt area are promptly coagulated. But many more are significantly damaged and become nonviable soon afterwards. In major burns this is often marked by the loss of fluid from the intravascular compartment, which results in severe hemoconcentration and an increased packed cell volume. It is only after the resorption of the extravasated fluid that the reduction in red cell mass becomes manifest. The loss of red cells may be as high as 10% of the total red cell mass per day in major burns. Constant and regular monitoring of the blood count is, therefore, essential in all burns.

Changes in white cell count occur according to the level of infection in the body. A reduction in platelet count is one of the earliest signs of impending sepsis. Transfusion of platelet concentrates as and when necessary and the use of appropriate antibiotics is indicated.

Coagulopathies may occur in the resuscitation phase. Disseminated intravascular coagulopathy is associated with reduction of various clotting factors including prothrombin, factors V, VIII and IX. Thrombocytopenia and thrombocytopathy necessitating platelet transfusions may be observed. A hypercoagulable state may occur 2–4 weeks after a severe burn injury.

Immunologic Effects

The host immune response is suppressed in severe burn injuries. Complement and immunoglobulin levels are initially depressed, and chemotaxis is initiated by the presence of a plasma inhibitor. Patients with burns are excessively prone to nosocomial infections, and in spite of the use of topical and systemic antibiotics, sepsis remains a major killer, particularly in poor developing countries.

Metabolic Effects

Increase in the metabolic rate with a markedly negative nitrogen balance is greater than in any other form of trauma. There is an increase in oxygen consumption and in carbon dioxide production. The stress response is mediated by catecholamines, other anti-insulin hormones, and is often associated with glucose intolerance in the early post-burn period. Insulin resistance may be observed over a prolonged period of time. Hypermetabolism increases with sepsis, cooling and pain, and control of the above-mentioned factors plays an important role in management.

First Aid

Burn injury is caused by heat. Even after the flames are extinguished, the residual heat trapped in the skin continues to damage the tissues. A burning sensation indicates the presence of heat in the tissues. Cold water (not ice cold) should be poured over the burnt area till the burning sensation has subsided. This may take up to 6 hours. Cooling the burnt area reduces both the area and depth of burn. It is the easiest way to reduce the burn damage to the tissues, and to reduce the pain. Analgesics and sedatives should be avoided, as the restlessness seen after burn injury is often due to cerebral hypoxia; sedation may actually accentuate the cerebral hypoxia, thereby increasing the restlessness. In chemical burns, the chemicals over the body should be washed away with copious amounts of water.

Transport

Loss of blood volume starts immediately following burn injury. It is most severe during the first 8 hours. In burns higher than 30% of total body surface area, the leakage of plasma occurs all over the body. This fluid volume deficit must be replaced as early as possible. While in transport, fluid replacement should be actively undertaken if the time taken to reach a burn center will take more than 1 hour.

Assessment of Burn Severity

The area of burns is estimated by the simple Wallace's "Rule of Nine" (Fig. 2). A more accurate and better method is the estimation by Lund and Browder's chart (Fig. 3).[7] Burns of over 10% body surface area in a child and over 15% body surface area in an adult can cause hypovolemic shock and hence should not to be taken lightly. Burns of over 30% of the body surface area are very serious.

Burn severity also varies with the depth of burn (Fig. 4). Burns which damage the full thickness of the skin are considered full thickness burns. When the depth of the burn is not complete, it is known as a partial thickness burn. Partial thickness burns heal by regeneration from the residual skin elements, if managed properly. Full thickness

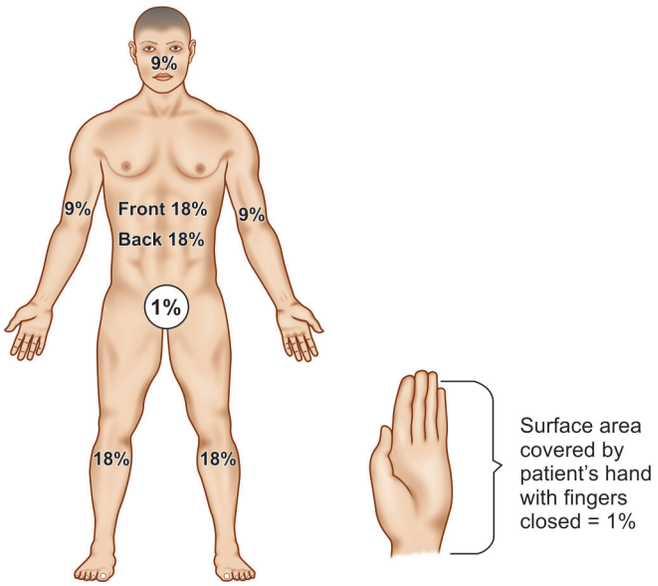
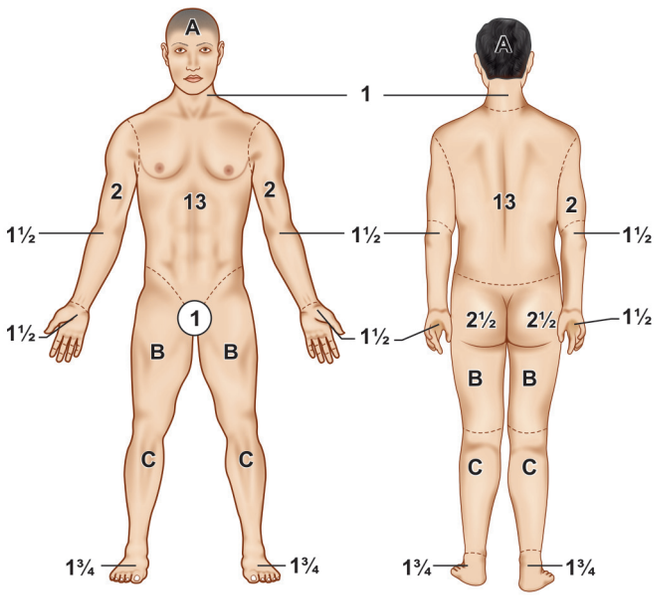


Fig. 2: Estimation of surface area by the Wallace's Rule of Nine



Area	Age	0	1	5	10	15	Adult
A = ½ of one thigh		9½	8½	6½	5½	4½	3½
B = ½ of one thigh		2¾	3¼	4	4½	4½	4¾
C = ½ of one leg		2½	2½	2¾	3	3¼	3½

Fig. 3: Estimation of extent of burns (%) by Lund and Browder's Chart[7]

burns always require a skin graft to heal. They are therefore more difficult to manage.

The depth of the burn is also dependent on the degree and duration of heat applied to the tissues (Table 1).[8,9]

IMMEDIATE MANAGEMENT

Hemodynamic changes outlined earlier occur rapidly following burns. These have to be anticipated and managed

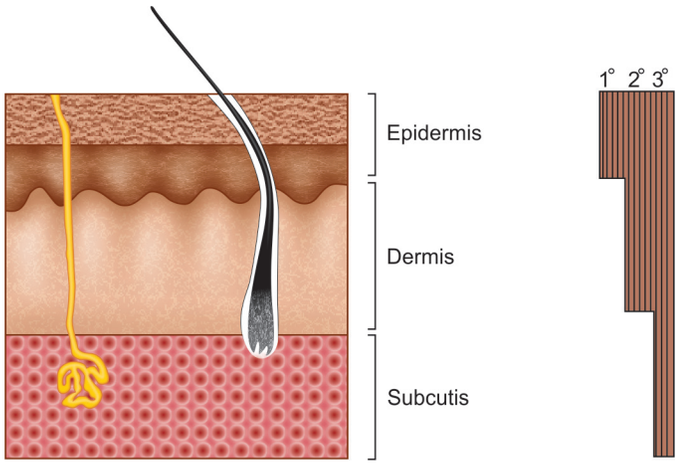


Fig. 4: Classification of burns according to the depth of injury

Table 1: Production of full thickness burns depends on degree and duration of heat applied to skin[8,9]

Temperature (°C)	*Time*
At 44	In 6 hours
At 59	In 60 seconds
At 62	In 30 seconds
At 65	In 20 seconds
At 70	In 10 seconds

appropriately. Burn patients have massive evaporative heat loss and hence need treatment in a room with increased temperature. Air conditioning, i.e. cooling of the atmospheric temperature, is contraindicated. The burnt skin exposes the underlying tissues to infection, and such patients need strict aseptic management. A well-equipped burn center staffed by specially trained personnel is an essential requirement for the management of these critically ill patients.

Management is best considered during the resuscitation phase (0–36 to 48 hours), the postresuscitation phase (36–48 hours to 5 days), and the phase of inflammation and infection (6 days to period of wound healing).

RESUSCITATIVE AND IMMEDIATE POSTRESUSCITATIVE MANAGEMENT[8]

The principles of therapy are—

- Fluid replacement and cardiovascular support to ensure maximum hemodynamic stability.
- Care of the airways and pulmonary support, as and when this becomes necessary.
- Correction of electrolyte and acid-base disturbances.
- Nutritional support.
- Care of the burn wound.
- Symptomatic treatment of pain and the use of antacids.

Fluid Resuscitation and Cardiovascular Support[6,10]

Several formulae are available and have strong proponents. The Parkland formula of Baxter is simple, practical and efficacious, has been adopted in most burn centers, and is currently the standard against which new formulae must be compared.[11]

First 24 Hours

Ringer Lactate solution, 4 mL/kg body weight per percent burn, is administered. The total burn area is used in the calculation. Half of the calculated amount is given in the first 8 hours. The urine output should be approximately 0.5–1.0 mL/kg per hour.

Second 24 Hours

Five percent dextrose and ringer lactate 0.5 mL/kg per percent burn are used. Colloids are administered after the first 24 hours by which time the capillary leak is generally sealed. Some units favor the earlier use of colloids, administering them after the first 6 hours. The amount of colloid administered depends on the degree of burns 0.25–0.5 mL/kg per percent of burn, or 20–60% of calculated plasma volume. Albumin is often preferred; the only drawback is that it is very expensive. Fresh frozen plasma, dextravan, hemaccel or lomodex may also be used. Colloids and crystalloids must be infused at a constant rate. The sodium requirement is about 0.5 mmoL/kg per percent burns.

As mentioned earlier, various formulae have been recommended for fluid resuscitation and the use of colloids in the first 48 hours post-burn resuscitation period. These should serve merely as rough guidelines, and fluid adjustments should be titrated against patient response. Fluid resuscitation can be considered appropriate if tissue perfusion is adequate. In a young patient, a pulse rate less than or equal to 120/minute, a systolic blood pressure more than or equal to 100 mm Hg, a mean arterial blood pressure of about 85 mm Hg, a urine output of at least 0.7–1 mL/kg, and absence of base deficit are parameters generally associated with adequate perfusion.

Renal and splanchnic blood flow are often selectively decreased during the first 24–48 hours after burns, and there is an increase in the secretion of aldosterone and antidiuretic hormone. We often use low dose dopamine (2 μg/kg per minute) to maintain the urine output, rather than pushing excessive intravenous fluids, when other parameters of adequate perfusion have been satisfied.

Fluid Replacement during the Post-resuscitative Phase (36–48 Hours to 5 Days)

This period is characterized by major fluid shifts. In deep burns, there is a continued loss of plasma into the burnt tissue. In superficial burns, there is a leak of plasma from the wound surface. The higher the capillary filtration pressure, the greater is the loss (Box 1). In addition, there is significant evaporative water loss from the wound surface. Five percent dextrose, alternating with dextrose saline is used to replace both loss of fluid from the burns, and evaporative loss from the wound surface. Hourly losses can be estimated from the formula—

Box 1: Fluid replacement in the post-resuscitative phase of burn injury (36–48 hours to 5 days)

- Replace evaporative water losses from wound surface and plasma loss into burn tissue with 5% dextrose alternating with dextrose saline
- Correct protein losses by albumin infusions, maintaining serum albumin >2.5 g/dL
- Correct anemia by packed cell infusions, maintaining hematocrit >30%

$$\text{mL/hr loss} = (25 + \text{percent of body surface burnt}) \times \text{m}^2 \text{ surface area}$$

Albumin may need to be continued to replace loss of plasma protein via the wound surface. Packed red blood cells may need to be given in patients with hemolysis, and for correction of anemia produced by impairment of red blood cell production in the bone marrow. Packed cells are preferred and it is advisable to keep the hematocrit more than or equal to 30%.

Monitoring volume replacement by the same tissue perfusion parameters described in the immediate 24–36-hour resuscitation period may be misleading after the first 3 days. This is because wound inflammation may commence around this time, and this produces a hyperdynamic circulatory state with marked tachycardia. The latter, if present at this stage, may not necessarily be due to hypovolemia. In addition, the solute products of damaged tissue cells often induce a well-marked osmotic diuresis, so that the urine output may be excellent. It is necessary to check the specific gravity of the urine during this phase. A high specific gravity in association with a high urine output generally indicates the need for more fluid administration.

Care of the Airways and Pulmonary Support[6]

It is vital to ensure that the airway is patent. An upper airway obstruction can develop suddenly with catastrophic results. Problems within the lungs and in the large or small airways are most frequent in patients who have suffered a smoke inhalation injury. Inhalation of smoke in a fire causing burns can lead to severe hypoxia causing immediate symptoms due to this hypoxic injury. Smoke inhalation injury can also cause upper airways obstruction from heat and chemicals. Symptoms of airways obstruction may be delayed for 6–24 hours. Lower airways and parenchymal injury from chemicals in smoke can produce symptoms within hours, or these may take days to manifest. Airway problems can also occur in patients with full thickness burns to the face and neck.

Indications for prompt endotracheal intubation include stridor, respiratory distress, PaO_2 less than 60 mm Hg on 4 liters

Box 2: Indications for endotracheal intubation in severe burns

- Stridor
- Respiratory distress
- PaO_2 <60 mm Hg on 4 L oxygen via mask/nasal prongs; $PaCO_2$ >50 mm Hg
- Deep facial or neck burns resulting in massive facial edema
- Upper airways edema
- Presence of airways injury-oropharyngeal edema/erythema, hoarseness of voice, changing respiratory status
- Severe chemical burns causing bronchoconstriction, bronchorrhea, acute lung injury

oxygen through a mask or nasal prongs, $PaCO_2$ higher than 50 mm Hg, and the presence of deep burns to the face and neck. A severe deep facial burn can lead to massive facial edema over the next 12–18 hours, so that intubation, if necessary at this time, can become difficult or impossible. It is therefore wise to intubate these patients electively at an early stage.

Even when none of the above indications are present it is important to look for signs of airways injury. If oropharyngeal edema is present, or the voice is hoarse an indirect laryngoscopy should be performed. Nebulization with racemic epinephrine helps to reduce local laryngeal edema. If racemic epinephrine is unavailable, adrenaline 1 in 1,000 dilution could be nebulized effectively. Adrenaline however often produces tachycardia. Nebulization with budecort could also help reduce laryngeal swelling and edema. Systemic steroids may also be used for a day or two; prolonged use is contraindicated as it predisposes to infection. If upper airway edema persists and causes airway obstruction, the patient should be intubated. If erythema alone is present without much edema, the patient will still need close observation. Any deterioration in respiratory status on a close follow-up merits securing of the airway by intubation. If endotracheal intubation is impossible because of edema and swelling of the airways, a tracheostomy needs to be done. A tracheostomy in severe burns is generally associated with high morbidity and mortality, but in some patients it is the only available option.

Endotracheal intubation is also often necessary in patients with severe chemical burns that cause bronchoconstriction, bronchorrhea, and acute lung injury. The indications for endotracheal intubation in severe burns are listed in Box 2.

Ventilator support should be offered in the presence of acute respiratory failure or in the presence of incipient respiratory failure. Acute lung injury (ARDS) may occur at any time but is generally observed after the first 5–6 days. When present, it requires the use of PEEP. The patient may need to be paralyzed with pancuronium to enable efficient ventilatory support to be given. It is advisable to adjust ventilatory support so that peak inflation pressures do not exceed 30 cm H_2O, as these patients are particularly sensitive to barotrauma, and pneumothorax may easily occur.

During the post-resuscitative phase (36–48 hours to 5 days), fluid present in the interstitial compartment due to tissue edema often shifts back into the vascular compartment. This can cause hypervolemia and worsen the acute lung injury (ARDS).

Optimal pulmonary support should always be given during and after any surgical procedure on the burn wound. Surgical procedures as far as possible should be of short duration and preferably not exceed 2 hours.

Nosocomial infection with nosocomial pneumonia is an important complication of ventilator support. It can occur at any time but is more frequent after the first week. Appropriate antibiotics are imperative as soon as a diagnosis of nosocomial pneumonia is made.

Injury from burns, particularly smoke inhalation injury, is sometimes complicated by CO poisoning and rarely by cyanide poisoning. These produce immediate symptoms. CO poisoning is associated with mental disturbances and obtundation. A high index of suspicion is necessary for a correct diagnosis. CO poisoning should be suspected if the measured oxygen saturation of Hb is less than that predicted by the PaO_2, and if the patient has metabolic acidosis with a wide anion gap. The diagnosis can be confirmed by a carboxyhemoglobin level higher than 5%. Continuous administration of 100% oxygen decreases the half-life of carboxyhemoglobin from 4 hours on air to about 80 minutes.[12] Cyanide intoxication may often be impossible to detect. Acute metabolic acidosis in the presence of a normal PaO_2 and a normal oxygen saturation of Hb should suggest the diagnosis. Anticyanide therapy includes the use of sodium nitrate, sodium thiosulphate and hydroxocobalamin.

Electrolyte Disturbances[6]

These are generally observed in the post-resuscitative period (from 36–48 hours to 5 days). The following electrolyte disturbances are commonly seen—

Hypernatremia

Hypernatremia is due to inadequate replacement of insensible water loss and the use of N-saline in intravenous infusions. Salt restriction and infusion of 5% dextrose should correct hypernatremia.

Hyponatremia and Hypokalemia

They may result from frequent washing or bathing of the burns patient with water, instead of an isotonic solution. Intravenous infusions of N-saline with potassium supplements will correct this situation. Severe hyponatremia may need a titrated infusion of 3% saline. Hypertonic saline should be avoided or used with great circumspection in the presence of pulmonary congestion.

Hyperkalemia

Hyperkalemia may occur in the early stages due to tissue damage and red cell destruction. Dextrose-insulin infusions help to reduce serum potassium levels. After 3–5 days, renal losses of potassium may be excessive so that potassium supplements of 80–200 mEq/day may be necessary.

Box 3: Composition of the buttermilk diet (BMD)

- Curd – 1 liter
- Eggs – 4
- Bananas – 4
- Sugar – 10 tablespoons
- Total volume – 1,760 mL
- Calories provided – 1,760 kcals
- Proteins – 60 g
- Carbohydrates – 340 g

Hypocalcemia

Hypocalcemia is invariably due to hypoalbuminemia. Intravenous albumin infusions, and correction of hypoproteinemia are then required.

Acid-Base Disturbances[6]

Severe thermal injury causes rapid acidosis. A combination of metabolic and respiratory acidosis exists in severe burns associated with smoke injury to the lungs. The metabolic component is due to tissues damaged by acid metabolites, and due to relative hypoxia. The respiratory component is related to smoke injury to the lungs, or due to hypoventilation in some patients. These need prompt correction, as acidosis has an adverse effect on myocardial function and on the overall circulatory system.

Nutritional Support[6,13]

Early oral feeding is now the preferred method of nourishing a burns patient. It should be commenced when resuscitation is complete, i.e. within 48–72 hours. As the patient will find it difficult to chew and masticate the food, liquid food must be specially prepared and given orally or through a nasogastric tube. Small measured quantities given hourly are preferable to infrequently administered large nutrient boluses. The buttermilk diet (BMD) is a well-tried and safe diet providing 1 kcal/mL. It is hence easy to monitor the amount of supplementary nutrition received by the patient. The composition of the BMD is given in Box 3. Starting with 10 mL/hour through the nasogastric tube, the quantity administered is increased by 10 mL per hour every 6 hours to reach a maximum of 2 mL/kg per hour for adults and 3–5 mL/kg per hour for children. Each feed is preceded by nasogastric aspiration to rule out gastric stasis and to prevent gastric dilatation. Some units prefer to administer enteral feeds by a continuous drip through a nasogastric tube, over a period of 14–16 hours. Generally, after a period of 96 hours post injury, the patient can be started on full diet with discontinuation of intravenous fluids.

In the presence of impaired GI function, parenteral nutrition is necessary. This may be total or partial. A daily protein intake of 2–2.5 g/kg per day generally suffices with a total caloric intake of 2,500–3,000 calories/day, the energy requirements being provided by dextrose and lipids (see Chapter Nutritional Support in the Critically Ill Adult). Vitamin supplements are necessary; hyperglycemia may require the use of insulin.

Local Care of the Burn Wound

Contamination of the burn and invasive wound infection is the most dreaded complication. The wound must be covered as early as possible with a clean sheet over which cool water is constantly poured to lower the temperature and withdraw heat from the wound. This helps to reduce the thermal damage.

Blisters or bullae should not be excised. They are just punctured and the fluid drained. If the bullae have already ruptured, the loose non-viable skin should not be excised, but cleaned with saline and evenly spread out over the burn. This non-viable skin serves to protect the burnt tissues underneath, and prevents desiccation of the wound.

Tetanus is an important complication of burns in poor countries. Tetanus toxoid should be given on admission. Patients who have not been previously immunized should be given 250 units of tetanus human immunoglobulin and active immunization with tetanus toxoid should be commenced.

Treatment of the Burn Wound[6]

The exposure method of treatment has now been abandoned in burn centers all over the world, and the closed method of treatment has been universally accepted and adopted. After adequate resuscitation, the patient is given a bath and is dressed in the operation theater. The choice of the antiseptic used over the burn wound varies. A silver sulphadiazine cream 1–2% is most frequently used. Mafenide acetate 10% cream or 5% solution is preferred in some units in the West as this is believed to penetrate the eschar. It is unavailable in India and the silver sulphadiazine cream probably does just as well.[6] Povidone Iodine in solution form, along with Vaseline gauze, is used in some centers.

The nature of the agent used to dress and cover the wound varies. The *potato peel dressing* has been found to be eminently suited for this purpose. It is smeared with an antibacterial ointment (silver sulfadiazine cream) and gently applied over the burnt area; it is held in position with a gauze bandage. To prevent it from slipping, a single wet layer of plaster of paris is spread over the dressing and allowed to dry into a thin shell, almost as thin as an eggshell, hence called the "Egg Shell Dressing". These dressings are changed once a day. Many prefer to use a "collagen dressing" to cover the wound. A very frequently used biological skin substitute is termed *Integra*. This is a totally artificial material which is acellular and composed of two layers. The upper layer is of silastic and the lower layer is a cross-linked co-precipitate of collagen that is bovine in origin, and chondroitin-6-sulfate which comes from shark cartilage. Once the burnt tissue is excised, the Integra is stapled in place. When the lower layer has been populated by host cells, the silastic layer can be

removed to provide an excellent vascularized mesodermal base. A freshly harvested thin epidermal graft can be laid on top of this to complete wound cover.

Cultured Autologous Epidermis[14]

A recent skin resurfacing technique is the use of cultured autologous epidermis to assist the timely closure of burn wounds. This technique requires expertise and special facilities, and to the best of our knowledge, it is still in the experimental phase in certain centers in India.

The technique consists of taking a full-thickness skin biopsy consisting of a few square centimeters. After an in vitro culture period of 3–4 weeks, the autologous population of keratinocytes expands to approximately 1 m^2 of keratinocytes that are available for wound coverage. Cultured autologous epidermis (CAE) has to be combined with dermal replacement in the form of integra, alloderm or cell-free porcine dermis.

There are however several shortcomings with this technique. These include—

- A relatively low rate of engraftment or "take" of each CAE application.
- Graft fragility resulting in delayed loss.
- Prolonged immobilization of extremities in order to facilitate engraftment, leading to loss of function.
- A very high cost when purchased commercially—about $2,000 for each percentage of wound closure.

This fact makes the above technique an impractical proposition for the poor countries of the world.

Whatever method is used to cover the burn wound, the joints must be positioned in their optimal functional positions with some form of splintage. Gentle active and passive physiotherapy of the limbs is instituted after 48 hours and progressively increased over the next few days to achieve maximum range of motion to prevent stiffness and contractures.

Escharatomy

It is not always possible for burn wounds in developing countries to be managed by the ideal, closed method of treatment. Through lack of facilities, burns are sometimes treated by the exposure method, and the patient is referred subsequently to a unit with better facilities. By the time of referral, the burn tissues on the surface have already formed a hard inelastic eschar. The edema which occurs in the underlying tissues following burn injury exerts an excessive compression on the vascular network, and impairs the circulation. Dry gangrene results very often as does anaerobic infection when the eschar is circumferential. Such an eschar around the chest wall restricts the respiratory excursions and impairs ventilation. Releasing incisions in the midlateral positions of the involved extremity or trunk have been recommended. The incisions should be made only through the eschar and subjacent tissue, lest the larger blood vessels are cut, resulting in excessive blood loss.

Escharectomy and Split Skin Grafting

When the eschar separates out and is replaced by healthy granulation tissue (usually at 2–3 weeks post-burn), the wound is debrided and covered with a very thin split skin graft, preferably meshed 1:3. Blood loss at the time of surgery is rapidly corrected, or better still, is reduced by subcutaneous infiltration of normal saline with adrenaline 1:1,000,000. Post-grafting dressings are done every 2–3 days thereafter.

Early Excision and Grafting of the Burn Wound[14]

When good facilities exist, i.e. trained surgical and nursing staff, facilities for good anesthesia, adequate dressing material and equipment, adequate supply of blood and homograft skin, the ideal treatment today consists of excision of all full thickness and deep partial thickness skin burns along with homografting, starting within a few hours after the burn injury is sustained. However, such conditions are available in a few of our burn centers and make a significant difference to outcome in terms of survival. Moreover, in children with scald burns, conservative management with dressings is preferred over early excision unless the wound is clearly full thickness.

Fascial Excision and Skin Grafting

This is indicated in severely infected burns with invasive burn wound sepsis (>10^5 bacteria/gm of burnt tissue on burn wound biopsy). All the dead and infected tissues up to the level of fascia are excised en bloc and the resultant raw area is skin grafted with autografts.

Symptomatic Treatment of Pain and the Use of Antacids[6]

A partial thickness wound is very painful. Also, the surface of a burn wound dries up if kept exposed, and the process whereby an eschar forms can be extremely painful. The application of a semipermeable membrane relieves pain to a great extent. A small dose of a combination of ketamine 100 mg, tramadol 100 mg and midazolam 10 mg in a 50-cc syringe in a syringe pump titrated against the patient's response is frequently used as a continuous intravenous infusion, to relieve the pain. We have found this combination works in the following doses: resting pain 2–6 mL/hour and procedural pain 20–40 mL/hour depending on body weight and response. Following a burn injury, acute stress often leads to upper GI bleeds from acute mucosal erosions and from a Curling's ulcer. Blood loss may be significant and may need to be replaced. Sucralfate or antacids may help in preventing or reducing the incidence of GI bleeds. In burns greater than 40%, an intravenous H_2-antagonist is routinely given during the first 2 weeks post-burn.

MANAGEMENT DURING THE PERIOD OF INFLAMMATION AND INFECTION[15]

The hypermetabolic response to injury takes the form of the systemic inflammatory response syndrome (SIRS) which

starts around the 5th day of burns, and peaks at 8–10 days. This response is not necessarily associated with infection, though infection is a frequent and dreadful complication. It is extremely difficult, and in the initial stages, often impossible to distinguish inflammation-induced hypermetabolism from an infection-induced process. This phase is the most dangerous and difficult to manage in severe burns.

Symptoms and Signs of Invasive Wound Infections

Systemic features include tachycardia, tachypnea, hyperthermia or hypothermia. Disorientation, ileus, hypotension, oliguria, glucose intolerance and acidosis may be present. Leukocytosis is frequent, but sepsis may cause severe leukopenia and thrombocytopenia. These systemic features are indistinguishable from sepsis produced by central line sepsis, fulminant urinary infections or nosocomial pneumonia. Physical changes in the appearance of the burn wound are therefore more reliable signs of invasive burn wound infection than systemic features. Clinical signs of burn wound infection include—

- Focal dark or black discoloration of the wound.
- Conversion of a second degree burn to full-thickness burn.
- Unexpected rapid eschar formation.
- Hemorrhagic discoloration of eschar fat.
- Edematous, inflamed, violaceous wound edges.
- Extensive foul smelling slough over the wound, with a greenish discharge suggesting a *Pseudomonas aeruginosa* infection.
- Abscess formation and infected lesions outside the burn wound area.

Surface cultures of the wound do not necessarily distinguish colonization from invasive infection. Quantitative cultures also lack sufficient sensitivity, though colony counts of less than 10^5 per gram of biopsy tissue correlates with absence of invasive burn wound infection. Histological examination of a biopsy of the wound and underlying viable tissue is the best method of establishing invasive infection. The presence of micro-organisms in viable tissue points to tissue infection.

Wound Management

Severe burn wound infection is treated by local and systemic antimicrobial therapy. Twice daily applications of 1% silver sulfadiazine ointment covered by sterile gauze dressings are used. Dressings such as Acticoat are available which can be left on for several days and help reduce the pain associated with the dressing. Systemic antibiotics should be promptly started in full doses to treat not only local and systemic sepsis but also to prevent the onset and progression of multiple organ dysfunction and failure. Organisms most frequently encountered in infected burns include pseudomonas, klebsiella, E. coli, acinetobacter, Staphylococcus aureus and Group A streptococci. We have generally found a combination of ticarcillin/clavulanic acid + an aminoglycoside + metronidazole to be effective. A proven or strongly suspected staphylococcal infection would necessitate the use of amoxicillin/clavulanic acid or vancomycin, teicoplanin. An alternative antibiotic regime for severely infected burns (chiefly due to Gram-negative organisms) is the use of imipenam-cilastin 500 mg intravenously eight hourly or meropenam 1 g eight hourly given as an intravenous infusion. Either of these can be combined with vancomycin 500 mg six hourly or 1 g twice daily or teicoplanin 400 mg once a day in an intravenous infusion to cover possible staphylococcal infection. Local or systemic fungal infection merits the use of fluconazole and/or amphotericin B (see later section in this chapter on Antifungal Treatment).

Broad guidelines for antibiotic usage are outlined below[15]—

- Colonization of a large burn wound surface is impossible to prevent and invariably occurs. The mere culture of organisms is no indication for antibiotic use, in the absence of clinical evidence of infection.
- When clinical (and in particular histological) evidence of wound sepsis is associated with growth of organisms from an unhealthy infected wound, the choice of antibiotics should be guided by culture and sensitivity reports. Gram-negative infections are most frequently responsible for wound infection and need an appropriate antibiotic cover.
- Antibiotics once chosen should be continued for at least 5–7 days to allow them to act properly. Yet prolonged use of the same antibiotics can cause the emergence of resistant organisms. Appropriate antibiotic change should again be guided by culture and sensitivity reports.
- The pharmacokinetics of antibiotics in severe burns is considerably changed. If possible, drug dosage should be adjusted to ensure adequate bactericidal serum concentration levels. Unfortunately, the penetration of antibiotics into a burn eschar is unreliable in spite of adequate serum concentration of the drug.
- The prophylactic use of antibiotics in burns should be reserved for—
  - Preoperative and perioperative administration associated with excision, debridement and autografting.
  - Early phases of burns in children (a practice in some units).
  - *Cases of infection* In poor developing countries, transport of patients with severe burns to an intensive care unit or to a burns unit is often done in an unhygienic fashion so that infection is almost certain to occur. When this is so, many units in the city administer prophylactic antibiotics from the day of admission. Till definitive swab culture and sensitivity reports are available, a combination of ampicillin and an aminoglycoside is administered intravenously. The wisdom of this is disputable, though most experienced specialists in burns in this country believe that under existing circumstances, morbidity is reduced.

It should be noted that the mere use of local and systemic antimicrobial therapy does not always suffice. Aggressive surgical debridement and resection of infected tissue may

occasionally be imperative. Bacteremia, severe systemic sepsis, and even septic shock may follow such a major surgical procedure, and should be anticipated. The importance of correct local treatment to the burn wound by topical antibiotics and aggressive excision prior to this phase cannot be overemphasized.

Fluid Replacement and Cardiovascular Support

Adequate fluid replacement should take into consideration evaporative water loss and loss of blood and plasma from debridement of necrotic tissue. The catabolic state results in high fever necessitating further increase in evaporative losses at a rate of 8–10% per degree of rise in body temperature. The hematocrit should continue to be kept at 35% by packed cell infusions, and the albumin concentration should be maintained at around 3 g/dL. The hyperkinetic circulatory state is associated with a marked increase in the cardiac output to meet the increased oxygen demands. Myocardial dysfunction often supervenes, and inotropic support with dopamine and other inotropes as also vasopressors may be frequently necessary. Cardiopulmonary failure in this phase of severe burns is most frequently observed in elderly patients. This is because the circulatory and respiratory systems in the aged have a comparatively limited reserve which is unable to cope with the excessive metabolic demands of the stress response induced by severe burns.

Respiratory Support

Nosocomial pneumonia is a frequent complication, and the increased metabolic rate leads to increased carbon dioxide production necessitating increase in ventilatory requirements. Respiratory muscle fatigue often supervenes, so that patients, who were breathing spontaneously, may now require ventilator support. Acute lung injury (ARDS) may also complicate the picture at this stage, and this worsens the prognosis markedly as it is often the forerunner of multiple organ failure.

Metabolic Support

Maintenance of adequate nutrition is vital for survival during this phase, as the hypermetabolic state leads to a severe loss in lean muscle mass. The enteral route is always to be preferred, and this may be supplemented, if necessary, by parenteral nutrition. Total parenteral nutrition may be required at times.

Care of the Eyes and Ears

For protection of the eyes from infection, antibiotic eye-drops during the day and antibiotic ointment at night may be used. Mydriatics may also be used.

Chondritis is a dangerous complication which may result in the whole ear falling off due to infective destruction. It is treated by providing adequate fluffy padding for burnt ears with adequate antibiotic cream cover to prevent pressure necrosis of the fragile infected cartilage; this is combined with radical debridement of the dead infected cartilage.

Control of Infection[15]

A combination of an immunosuppressed host and bacterial colonization of the burn wound, the oropharynx and the tracheobronchial tree strongly predisposes to nosocomial infection. Nosocomial pneumonia, vascular catheter sepsis, urinary catheter sepsis and, above all, deep severe infection of the burn wound are all too common, and can trigger multiple organ failure.

A diagnosis of nosocomial pneumonia should be based on clinical and radiological grounds. Leukocytosis, fever, purulent sputum, or purulent tracheal aspirate showing many organisms on Gram stain, with an increase or change in pulmonary shadowing, suffice to make a clinical diagnosis. Empiric antibiotic treatment should not be delayed pending sputum culture sensitivity reports.

If possible, vascular catheter sepsis should be prevented by change of the central lines (every 7–10 days), by prompt removal of the arterial lines, and by avoiding the use of a Swan-Ganz catheter, unless this is absolutely necessary. Catheter tips should be sent for culture, and blood cultures should always be done in each and every patient with nosocomial infection, so as to enable a proper choice of antibiotic therapy.

Antifungal Treatment

Invasive fungal infection of the burn wound and/or systemic fungal sepsis are important complications, particularly in extensive severe burns. They carry a high morbidity and mortality. Candida species frequently colonize a burn wound but rarely cause an invasive wound infection. Aspergillus however can cause an invasive fungal wound infection which generally is limited to subcutaneous tissue and only rarely crosses fascial planes. Rarely fungal invasion of the wound by Mucor species may also occur. Colonization of a burn wound with Candida or Aspergillus can be countered by the local application of clotrimazole. However, if there is histologic evidence of fungal invasion of the wound, treatment consists of wound debridement and excision, and the use of intravenous amphotericin.

Systemic fungal sepsis with positive blood culture for fungi is either nosocomial through vascular catheters, or results as a superinfection due to prolonged use of broad-spectrum antibiotics, or results from vascular invasion. Fluconazole and/or amphotericin or caspofungin need to be given in an intravenous infusion. Some units use fluconazole prophylactically in situations where fungal infection is strongly anticipated.

Treatment of Complications and Support of Multiple Organ Systems

All organ systems need to be carefully supported. Renal failure may require dialysis. A progressively increasing serum creatinine and a progressively increasing blood urea nitrogen may necessitate dialysis regardless of the volume of urine excreted.[16] Bacterial infection is a frequent hazard and

complication, and death often results from infection rather than from renal failure.

Prevention

Burns treatment is far more advanced now than it was 50 years ago. The mortality and morbidity are much lower, but the pain suffered and the dreams shattered are as real as before. The basic aim or objective is to prevent burns. A great deal of research needs to be done in this direction for this objective to be adequately realized.

Rehabilitation

Physiotherapy is very important to maintain function. Pressure garments may be used to prevent hypertrophic scar formation. Moisturizing agents to soften scars and steroid creams to decrease itching are also commonly used. The use of silicon gel sheets to soften scars has been found to be useful. Quite often, for small linear scars, injection of triamcinolone acetonide given intralesionally in multiple doses spread over months helps.

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CHAPTER 66

Critical Care in Poisonings

GENERAL CONSIDERATIONS

The evaluation and management of a patient, who intentionally or accidentally ingests or is exposed to a poison, is an important aspect of critical care medicine. There are a vast number of poisons; important poisons include drugs which in toxic doses produce dangerous and often life-threatening effects.

The diagnosis of acute poisoning though often obvious is at times difficult. The possibility of poisoning should always be considered in any obscure illness, or in any patient in whom the cause of unconsciousness is not clearly apparent.

Critical care of patients acutely ill with poisoning as a matter of urgent priority necessitates life support to keep them alive. Prevention of absorption of poisons, their quick elimination, and the use of specific antidotes are of further help in a number of situations.

This chapter outlines the principles of approach to poisonings in patients admitted to a critical care unit. It then briefly outlines the clinical features and management of a few important and common poisonings, particularly those observed in our part of the world.

PRINCIPLES OF APPROACH TO A POISONED PATIENT[1,2]

- First and foremost attention should be focused on the airway, breathing and circulation (ABC).
- Intravenous access is secured and blood tests sent, both routine laboratory tests and tests for possible poisons. An intravenous (IV) infusion of N-saline or Ringer lactate is started; hypotension is corrected initially with a volume load.
- If the patient has an altered mental state or is comatose, potentially reversible causes need to be promptly excluded—
  - Hypoglycemic coma is promptly reversed by a rapid IV infusion of concentrated glucose.
  - Acute deficiency of B1 is promptly reversed by IV 100 mg thiamine.
  - Opioid toxicity is reversed by IV Naloxone 0.2–4 mg.
- If the poisoned patient is admitted with seizures, it is important to control seizures by the use of appropriate IV anti-seizure drugs. The possibility that a more specific antidote may be necessary should however be kept in mind.
- *Diagnostic Evaluation* A careful history and detailed physical examination is necessary. The physical examination should determine if the poisoned patient falls into any one of the well recognized toxidromes. If such a diagnosis can be made an appropriate antidote should be given provided it is available.
- An attempt should be made to block the absorption of the poison and to enhance the elimination of the poison when appropriate.

The above principles are now briefly discussed and this discussion is followed by a discussion on specific important poisons and their management.

ATTENTION TO THE AIRWAY, BREATHING AND CIRCULATION

Airway, breathing and circulation need to be given prime immediate attention. If the patient is admitted to the ICU with a cardiac arrest or a near cardiac arrest, attention should first go to the resuscitation of the heart which is then promptly

followed by attention to keeping the airway open and ensuring breathing (see Chapter Cardiopulmonary Resuscitation and Cerebral Preservation in Adults).

Airway, Breathing and Respiratory Care

A blocked airway (chiefly with secretions), a loss of airway reflexes, respiratory depression and aspiration are frequent consequences of poisoning.

The airway should be kept open, the neck should be extended and the jaw pushed forward and secretions sucked from the back of the throat. Endotracheal intubation is promptly done if: (i) the patient is deeply obtunded or unconscious; (ii) swallowing is impaired; (iii) the cough reflex is poor or absent, the patient being unable to protect his airway; (iv) the patient requires ventilator support either because ventilation is poor or because of pulmonary edema.

Oxygen should be given in 100% concentration. It can never do harm as an initial life-support measure. The only relative contraindication is in patients with paraquat poisoning. In the latter situation, very high concentrations of oxygen can promote pulmonary fibrosis.

Ventilator support is necessary in patients with acute respiratory failure, i.e. in those with hypoxia and/or hypercapnia. Ventilator support should also be offered in those with incipient respiratory failure, i.e. in acute poisoning known to rapidly lead to acute respiratory failure. The use of prophylactic positive end-expiratory pressure (PEEP) is unwise; PEEP should however be given in patients with poison induced pulmonary edema resulting from increased capillary permeability.

Care of the Circulation

The circulation should be assessed *pari passu* with respiration. A large peripheral vein is promptly secured; a central venous line is also invariably necessary in acutely ill patients to determine central venous pressure, and to thereby allow adjustments for volume load. A self-retaining Foley's catheter is passed to enable the urine output to be monitored hourly. Hypotension should be immediately corrected as this causes poor tissue perfusion, metabolic acidosis and worsens prognosis. Hypotension in acute poisoning may be due to a variety of causes acting singly or in combination. These include a decrease in systemic vascular resistance causing arteriolar dilatation, venous pooling, myocardial depression and hypovolemia. The initial management (except in the presence of pulmonary edema) is a fluid challenge of 200 mL of a crystalloid solution. Repeated challenges are given, provided the central venous pressure (CVP) is not beyond 10 mm Hg, the arterial blood pressure rises and the urine output is close to 60 mL/hour. If a volume challenge fails to raise the blood pressure, and the CVP is at the upper limit of normal, the patient is given dopamine and/or vasopressor support so that the systolic blood pressure is kept over 100 mm Hg and preferably around 120 mm Hg. The principles of inotropic and/or vasopressor support in patients with severe myocardial depression are the same as in patients with cardiogenic shock.

Use of Emergency Drugs

Two important causes of deep coma or of mental obtundation with or without hypotension are severe hypoglycemia and narcotic poisoning. For diagnostic and therapeutic purposes, it would be justified in giving first 50 g of dextrose intravenously to reverse possible hypoglycemia. Blood is collected for blood glucose estimation before dextrose is administered. This can do no harm and produces a magical response in patients whose coma is due to very low blood sugar levels. 100 mg of thiamine are generally administered to prevent Wernicke's encephalopathy, particularly in alcoholics who are admitted with severe hypoglycemia.

If intravenous dextrose produces no response, many critical care units would give a diagnostic and therapeutic trial to naloxone, a specific antagonist to narcotics. The initial dose is 2 mg intravenously. Improvement in respiration occurs in 2 minutes. Repeated dosing may be necessary, as the half-life of naloxone is shorter than the half-life of the narcotic agent. Some synthetic opiates (meperidine or propoxyphene) may require higher initial doses (6–8 mg) for reversal.

Control of Seizures

A few poisons can produce frequent or continuous seizures. These can be life-threatening and need to be controlled. Benzodiazepines should be used initially; phenytoin, valproate or other anti-epileptics may be needed if diazepam or lorazepam is ineffective. In refractory cases, intravenous thiopental or the use of paralytic curare-like agents may be necessary to allow efficient ventilator support. It is however important to note that control of seizures may occasionally require therapy specific to the poison involved.

DIAGNOSTIC EVALUATION[1-3]

Principles

- One should always entertain the possibility that the patient has ingested more than one poison.
- In case of an overdose of a drug, again the possibility of polysubstance overdose must be kept in mind.
- If the nature of the ingested drug or poison is known, an antidote if available should be promptly given. The lethal ingestion of the following drugs which have specific therapies should be ruled out if immediate facilities to do so are available. These are—
  - Tricyclic antidepressants (detected by a urine screen and ECG).
  - Acetoaminophen (detected by serum level).
  - Salycylate (detected by serum level).
- It is important to take a detailed history and perform a detailed physical examination to help determine the nature of the poison. As mentioned earlier, the physical examination should be detailed but should be oriented toward determining whether the findings are compatible with one of the toxidromes that will be described later.

History

A history is impossible in an obtunded or comatose patient. Even otherwise it is often unreliable, particularly when a drug is taken with suicidal intent. It is important to question relatives, friends and coworkers to obtain as much information as possible. Vital clues may be given by the presence of specific drugs or poisons found at the site of a patient's home or workplace.

Physical Examination

A quick physical examination may give a clue as to the nature of the poison. Physical examination is initially toxidrome oriented, which means oriented toward detection of symptom complexes that are associated with different groups of poisons. The following features are quickly evaluated—

Vital Signs

Sympathomimetic drugs, anticholinergics often produce tachycardia, hypertension. Anticholinergics produce a dry hot skin; cocaine can also produce hyperthermia, but with diaphoresis. Sedative-hypnotics or narcotics can produce respiratory depression, bradycardia and hypotension.

Brief Neurological Examination

It should determine the level of consciousness, the presence and nature of hallucinations, pupillary and motor responses.

Level of consciousness In severe poisonings with narcotics, hypnotics and sedatives, the patient is obtunded or comatose. Confusion, agitation and coma can also occur with poisons with a cholinergic action (e.g. organophosphorus compounds), as also with drugs that have an anticholinergic action (tricyclic antidepressants).

Hallucinations These are frequently seen in atropine and *dhatura* poisoning, in poisoning with cocaine, phencyclidine and LSD. With cocaine, hallucinatory objects appear in the periphery of vision; with atropine, hallucinatory objects are small; *dhatura* poisoning is associated with finger picking movements, as if the patient is pulling threads from his fingertips; complex hallucinations characterize poisoning due to phencyclidine; lysergic acid diethylamide (LSD) poisoning is associated with visual and auditory hallucinations and illusions where the patient can "hear colors" or "see sounds".

Pupillary responses Miosis can be caused by organophosphate insecticides and by narcotics. Though opium and morphine cause pin-point pupils, in almost all such patients a very strong focused light produces a small contraction of the pupil, demonstrating the integrity of the third nerve and that portion of the midbrain concerned with the pupillary reflex. Both atropine and cocaine can result in mydriasis, though in cocaine poisoning, the pupil will react to light.

Nystagmus Alcohol, sedatives-hypnotics and anti-epileptics, like phenytoin, primidone, can all cause nystagmus. Lithium poisoning and poisoning with carbamazepine and solvents also produce nystagmus.

Motor response Seizures can be induced by a number of poisons. The only important poison which can produce recurrent seizures with the patient remaining alert, and with muscle tone being normal in between seizures, is strychnine. Drug-induced seizures often respond poorly to conventional antiepileptic therapy. Thus isoniazid-induced seizures (invariably associated with mental obtundation or psychosis) will respond to pyridoxine, and seizures induced by tricyclic antidepressants will respond to physostigmine.

Auscultation of the Lungs for Pulmonary Edema and Bronchospasm

A number of poisons can induce pulmonary edema; cholinergic drugs can induce severe bronchospasm and an increase in bronchial secretions. This is important both from the diagnostic and therapeutic points of view.

Auscultation of the Abdomen for Bowel Sounds

Bowel sounds are feeble in severe sedative or narcotic poisoning; hyperperistalsis and abdominal cramps (if the patient is conscious) are observed with cholinergic poisons.

Skin Temperature and Moisture

Sweating is frequently observed with poisons having a cholinergic and sympathomimetic action. The skin is dry and hot in persons with an anticholinergic effect.

Important features in physical examination in relation to "toxidromes" or symptom complexes produced by poisons which exert a sedative-hypnotic effect, or an opioid effect, or a cholinergic effect, or an anticholinergic effect or a sympathomimetic effect or cause extrapyramidal features are charted in Table 1.

Laboratory Investigations

Blood glucose estimation is important in any individual who is obtunded or comatose. Routine investigations should include a blood count, urine examination, serum electrolytes, urea, creatinine, determination of the degree of anion gap, serum osmolality, calculated osmolar gap, liver function tests, X-ray chest, ECG, arterial blood gas analysis. The patient needs to be continuously monitored if there are arrhythmias. The QT interval should be measured, as an increase in this interval produced by a number of drugs can precipitate serious rhythm disturbances. Other laboratory tests depend on the specific poison suspected in a given patient.

Specific drug levels for drug intoxication due to specific suspected drugs may need to be done if facilities are available. Drug levels of salicylates, barbiturates, ethanol, digoxin, iron, theophylline and lithium are done in our laboratories. Serum levels of any of these drugs in suspected poisoning help management. Estimation of blood levels of most common poisons is now possible at one of the medical centers in Mumbai.

Table 1: Clinical toxidromes observed with common poisons, drugs.

	Clinical features	*Drugs, poisons*
Sedatives-hypnotics	Central nervous system (CNS) depression, drowsiness, coma, slow shallow breathing, hypotension, bradycardia	Barbiturates Benzodiazepines Alcohols
Opioid	Hypopnea, slow respiratory rate, pin-point pupils CNS depression—drowsiness, coma, hypotension, bradycardia, hypothermia, pulmonary edema	Morphine Heroin Meperidine Codeine Oxycodone Fentanyl Methadone
Anticholinergic	Mydriasis, tachycardia, tachypnea, hyperthermia, agitation, delirium, dry hot skin, dry mouth, urinary retention	Tricyclic anti-depressants Antihistamines Atropine Belladonna Phenothiazines
Sympathomimetic	Tachycardia, hypertension, tachypnea, diaphoresis, mydriasis, agitation, hallucinations	Cocaine Amphetamines Ephedrine Theophylline Caffeine
Cholinergic	Salivation, lacrimation, diarrhea, vomiting, increased urinary frequency, abdominal cramps, miosis, bradycardia, bronchospasm, confusion, coma	Organophosphates Physostigmine Pyridostigmine Edrophonium
Extrapyramidal	Rigidity, tremor, trismus, torticollis, oculogyric crisis	Prochlorperazine Chlorpromazine Haloperidol Other antipsychotic drugs

Toxicological screening tests must be interpreted with circumspection. Qualitative urine or screening assays may point to exposure to various drugs but cannot discern whether the exposure is responsible for the clinical presentation. Many substances are not included on screens that qualitatively assay drugs of abuse. False negative results may be reported depending on the sensitivity of the drug test, on the time of ingestion of a drug, the co-ingestion of more than one drug even in the presence of intoxication. Therefore, toxicology screens should be used to support clinical suspicion but management strategies should be guided by the history, clinical findings and the identification (if possible) of a toxidrome.

Specific poison can be identified by attention to the anion gap, osmolar gap.

$$\text{Anion gap} = [Na^+] - ([Cl_2^-] + [HCO_3^-])$$

The normal anion gap ranges from 7–13 mEq/L varying with different laboratories. An increased anion gap may indicate ingestion of ethylene glycol, methanol or salicylates. Causes of an increased anion gap are listed in Table 2. The osmolal gap is the difference between measured and calculated osmolality. An increased osmolal gap points to the presence of an osmolitically active substance in the blood, which is not accounted for by routine calculation of osmolality. Poisons causing an elevated osmolal gap include methanol, ethylene glycol, paraldehyde and formaldehyde (Table 3).

Table 2: Causes of an increased anion gap

Poisonings	*Medical problems*
Salicylate (Aspirin)	Lactic acidosis
Methanol	Ketoacidosis
Ethylene glycol	Diabetic ketoacidosis
Iron	Alcohol poisoning
Isoniazid	Starvation
Paraldehyde	Ureteric anastomosis into the colon

Table 3: Increased osmolar gap

With a normal anion gap	*With a raised anion gap*
Isopropanol	Methanol
Mannitol	Ethylene glycol
Acetone	Paraldehyde

An oxygen saturation gap should also be looked for. Oxygen saturation as measured by the pulse oxymeter significantly lower than the oxyhemoglobin percentage (SaO_2) as calculated from the arterial PaO_2 indicates carbon

Table 4: Common poisons and their antidotes

Common poisons	*Antidote*	*Dosage*
Opiates (morphine, heroin, codeine)	Naloxone	0.4–2 mg IV bolus; can repeat to maximum of 10 mg (see text)
Organophosphorus compounds	Atropine + Pralidoxime	2 mg IV repeated every 5 minutes till total of 10 mg 0.5–2 g IV over 5–15 minutes; can be repeated every 6–12 hours
Cyanide	Sodium nitrate	300 mg IV over 2–5 minutes
Ethylene glycol	Fomepizole	15 mg/kg over 30 minutes; then 10 mg/kg 12 hourly x 4 doses; then 15 mg/kg 12 hourly as needed
Iron	Deferoxamine	5–15 mg/kg per hour Maximum daily dose 6–8 g/day
Methanol	Ethanol or fomepizole	Same as in ethylene glycol
Carbon monoxide	100% oxygen; hyperbaric oxygen	
Isoniazid	Pyridoxine	1 g for each of isoniazid ingested or 5 g maximum; infused IV at 0.5 g/min till seizures stop; remaining infused over 4–6 hours
Digoxin	Digoxin-specific antibody fragments	10–20 vials for acute poisoning 4–6 vials for chronic poisoning
Methemoglobinemia	Methylene blue	1–2 mg/kg IV over 5 minutes followed by 30 mL saline flush
Acetaminophen	Acetylcysteine	See text
Tricyclic antidepressants (TCAs)	Soduim Bicarbonate	1.2 mg/kg IV followed by 150 mEq in 1 L 5% dextrose at 2.5 mL/kg/min

monoxide, cyanide or hydrogen sulfide poisoning, or the presence of methemoglobinemia. A spectrometric analysis of the blood can measure the concentration of oxyhemoglobin, deoxyhemoglobin, methemoglobin, sulfhemoglobin and confirm the nature of poisoning.

Imaging Studies

A plain X-ray of the abdomen may show the presence within the gut of radiopaque drugs, iron tablets or enteric-coated tablets. These films also visualize drug packets in patients who ingest the latter to smuggle drugs through customs.

History, clinical examination and relevant investigations should help diagnosis. Differential diagnosis of acute poisoning includes acute infections, particularly those involving the neuraxis, and metabolic problems, in particular hypoglycemia, hypercalcemia, liver and renal cell dysfunction. Head injury (when no wound is visible) can also mimic poisoning, as can a cerebrovascular accident particularly when the latter involves the brainstem. The neurological features produced by cyanide poisoning which is not immediately fatal, resemble brainstem infarction or the effects of severe hypoxia.

MANAGEMENT[4]

Life support, with a quick clinical assessment, and laboratory help to determine the nature of the poison are now followed or accompanied *pari passu* by measures to prevent absorption, use of a specific antidote when this is available, and measures for removal of absorbed poison.

Use of Specific Antidotes

Comparatively very few poisons have specific antidotes. Therefore, it needs to be stressed that in the majority of poisons the treatment is largely supportive and symptomatic together with an attempt to prevent absorption or increase elimination of the poison as far as is feasible. Important antidotes to specific poisons are listed in Table 4.

Gastrointestinal Decontamination

Gastrointestinal decontamination in a poisoned patient can be carried out through gastric emptying procedures (induced vomiting, gastric lavage), adsorption of drugs using activated charcoal and increasing transit through the gastrointestinal tract by catharties or whole bowel irrigation. The current belief is that other than the use of activated charcoal to adsorb poisons, there is very little use of other interventions.

Gastric lavage[5] is used infrequently today and that too only in patients who are brought to treatment within 1–2 hours after ingestion of the poison. A large orogastric tube is inserted into the stomach with the patient in a propped up position (to reduce the risk of aspiration). Lavage is given with 100–200 mL alliquots of normal saline till all stomach contents (which should be preserved) are washed out. An obtunded, drowsy or comatose patient should be intubated before lavage so as to protect the airways. Complications include aspiration pneumonia, esophageal perforation and cardiovascular instability. Gastric lavage is contraindicated in poisoning with acid, alkali, hydrocarbons, in patients with bleeding diatheses and in patients who are rowdy and very restless.

It is currently believed that gastric lavage offers no clear benefit even when the patient presents within 1 hour of ingestion of the poison and should not be employed routinely in the treatment of poisoned patients. We restrict its use to a patient who has swallowed a large life-threatening amount of poison and when lavage can be given within 60–90 minutes of ingestion, or when it is likely that the toxin is present in the stomach.

Induced vomiting and the use of cathartics are procedures of a past era.

The use of activated charcoal[6] is becoming increasingly popular in the management of acute poisoning. Activated charcoal is an inert non-toxic adsorbent which binds high molecular weight compounds due to intermolecular attractions. Although activated charcoal binds many compounds, there are several potential poisons that do not bind well. These include bromides, caustics, alcohol, methanol, ethylene glycol, lithium and isopropyl alcohol. When activated charcoal is used in repeated doses, it can interrupt enterohepatic circulation and hence enhance the elimination of drugs whose pharmacokinetics includes enterohepatic circulation.

The efficacy of activated charcoal is greatest when given within 1 hour of the ingestion of the poison. Activated charcoal is administered in a dose of 1 g/kg in adolescents or adults, mixed in lemon barley or water or fruit juice and is either drunk or given through a nasogastric tube. When used in repeated doses[7] to interrupt enterohepatic circulation of a poison or drug, 25 g is given every 2–4 hours in adults. In children 0.25–1 g/kg is given every 2–4 hours. Constipation can result from the use of activated charcoal. A laxative like magnesium sulfate should be added to the first dose of activated charcoal to counter constipation. Drugs amenable to repeat dose charcoal therapy include carbamazepine, diazepam, digoxin, phenobarbitol, phenytoin, salicylates and tricyclic antidepressants.

Contraindications to the use of activated charcoal include an unprotected airway, poisoning by a hydrocarbon. The presence of a major GI pathology or recent GI surgery is a relative contraindication.

Use of Whole Bowel Irrigation

Whole bowel irrigation (WBI) involves the administration of a large volume of osmolically balanced polyethylence glycol electrolyte solution to induce diarrhea and rapid expulsion of the poison from the GI tract. The procedure is performed through a nasogastric tube. The recommended regime has been 1.5 liters enterally administered WBI fluid in an hour. This is repeated till the rectal effluent is clear. Though WBI is used perhaps in many units in the West, we have never used this method for evacuation of an ingested poison. It is a taxing procedure for the patient, particularly in elderly enfeebled individuals and is not recommended for routine use. It is contraindicated in the presence of an unprotected airway, ileus, bowel perforation or obstruction, GI bleed, colitis, persistent vomiting and hemodynamic instability.

Toxins and poisons can also enter the body through the skin, and through the ocular, pulmonary and parenteral routes. In ocular exposure the eyes should be irrigated with N-saline for 30–40 minutes. Contamination of the skin with poisons should be countered by removal of the poison with soap and water. This is especially important with reference to organophosphates, hydrocarbons and herbicides. Separate drainage areas should be provided to dispose off the contaminated water used for cleansing the skin.

Elimination of Drugs or Poisons

The three methods to eliminate the drug or poison are: (a) use of multiple dose of activated charcoal (MDAC); (b) Alkalinizing the urine to enhance renal elimination of certain poisons; (c) use of extracorporeal methods, hemodialysis and hemoperfusion.

The use of multiple dose of activated charcoal has already been commented upon. Poison or drugs are eliminated if the drug or poison diffuses from the blood into the gut where it is adsorbed by the activated charcoal. A similar adsorption occurs in drugs or poisons which have an enterohepatic circulation. Drugs which have a long elimination half life, low protein binding and a low volume of distribution are best suited for MDAC use.

Renal elimination of certain drugs or poisons can be achieved by alkalinizing the urine to a pH more than 7. This is brought about by an attempt at forced diuresis with IV fluids which includes IV infusion of sodium bicarbonate (1–2 mEq/kg IV) during 3–4 hours. In our opinion this is rarely necessary. If used, it should be reserved for specific poisons, fluoride, salicylates, barbiturates, chlorpropamide, methotreate and primidone. Fluid diuresis with alkalinization of urine should be avoided in older people as it can cause pulmonary edema. Hyponatremia, hypokalemia and a rise in intracranial pressure are other complications.

Hemodialysis and hemoperfusion[8] These methods are increasingly used to enhance elimination of poisons and drugs. Indications include patients refractory to other methods of treatment, those with extremely high levels of the poison in the blood necessitating quick removal, those in whom other routes of elimination are impaired (e.g. patients with renal and hepatic insufficiency), in severe toxicity from drugs that can be faster removed by extracorporeal method than by other forms of therapy. It is important that hemodialysis and hemoperfusion are used when poisons are capable of being removed by this form of therapy.

A list of important poisons whose elimination is enhanced by multiple dosing with activated charcoal hemodialysis and hemoperfusion is given in Table 5.

MANAGEMENT OF SPECIFIC POISONING

OVERDOSE OF HYPNOTICS-SEDATIVES[1-3]

This is a common poisoning particularly in the comparatively affluent strata of society in India. Hypnotic sedative drugs

Table 5: Selected toxins removal by hemodialysis and hemoperfusion

Hemodialysis	*Indications*
Methanol	Severe acidosis, renal failure, impaired vision; level >40 mg/dL
Ethylene glycol	Severe acidosis, seizures, obtundation; level >40 mg/dL
Salicylates (aspirin)	Severe acidosis, renal failure, hemodynamic instability, central nervous system features; level >100 mg/dL
Calcium channel blockers (nifedipine, nimodipine, nicardipine	Severe cardiotoxicity, conduction defects, refractory hypotension
Beta-blockers (sotalol, atenolol, acebutolol)	Refractory hypotension, heart block, marked bradyrhythm, renal failure
Lithium	Renal failure, cardiovascular system instability, seizures, coma
Hemoperfusion	*Indications*
Barbiturates	Severe refractory hypotension, renal failure
Carbamazepine	Ingestion of a life-threatening dose, deep coma, severe cardiorespiratory failure
Theophylline	Seizures, recurrent arrhythmias; refractory hypotension
Valproic acid	Increasing hepatic dysfunction, deep coma with severe hypotension, levels >1000 mg/dL

include barbiturates, all benzodiazepines and alcohol. Barbiturates and benzodiazepines are frequently involved in overdosage, and are generally taken with suicidal intent. The poisonous effect of a large dose of barbiturates is often potentiated by alcohol, by the simultaneous use of narcotics like opium, or by the ingestion of tranquilizers and antidepressants.

Clinical Features

Clinical features are characterized by progressive depression of the central nervous system (CNS) culminating in paralysis of the brainstem and medulla. In the early stages, or in cases with mild overdose of sedative-hypnotics, there is ataxia and dysarthria with an altered sensorium, the clinical picture resembling acute alcoholic intoxication. Progressive depression of the CNS leads to stupor, followed by deepening coma. By the time the patient is in coma, his deep reflexes are not elicitable. There is flaccidity of the limbs, corneal reflexes are lost, conjugate doll's eye movements are absent, the pupils are dilated, and the respiration is feeble, shallow and irregular. Hypotension may be a prominent feature. These features signify severe depression of the brainstem and medulla. It is important to note that quite often a slight reaction of the pupils to a very strong light can be observed even when the patient has all other features of medullary paralysis. Death occurs from respiratory failure, severe hypotension due to vasomotor failure. Non-cardiogenic pulmonary edema may be observed. Hypothermia aggravates shock and hastens the end. Oliguria with renal failure can also occur.

Lethal Dose

The lethal dose of barbiturates cannot be stated with certainty. Short-acting barbiturates on the whole are more dangerous than long-acting ones. Blood levels compatible with a fatal outcome have varied from 10 mg/100 mL in long-acting barbiturates, to 3 mg/100 mL in short-acting barbiturates. However, patients with much higher blood levels have recovered, so that the finding of a raised barbiturate level in the blood does not necessarily constitute a prima facie evidence of death from barbiturate poisoning.

Diagnosis

The intensivist must bear in mind the numerous other causes of coma. It is important to ascertain that coma is not due to structural damage or organic disease within the brain. It is equally important to exclude all metabolic problems that can cause an impaired conscious state. The usual routine tests required for proper care have already been detailed earlier. Arterial blood gas analysis and a chest X-ray are both mandatory. A blood sample should be sent for estimation of barbiturate, bromide, glutethimide and phenothiazine levels.

Ingestion of non-barbiturate sedatives, such as chloral hydrate, glutethimide, methaqualone should be given differential consideration. Co-ingestion of alcohol, benzodiazepines is not uncommon in barbiturate poisoning with suicidal intent.

Management

This is based on the principles outlined above.

Cardiorespiratory Support

It is imperative in severe poisonings. Coma calls for prompt intubation. It is important not to wait for the PaO_2 to fall to 60 mm Hg before initiating ventilator support. Ventilatory support is given to a comatose patient not only for airway control but in anticipation of impending, worsening respiratory failure. Many of these patients have a dramatic and fairly abrupt fall in the PaO_2 to dangerously low levels, as also an abrupt rise in the $PaCO_2$. This should be anticipated and not awaited. Early ventilator support is therefore strongly advocated.

Gastric Lavage

This should be done once ventilation and circulation are stable, provided the patient is brought within 2 hours of ingestion of the poison. Lavage in an unconscious patient should always be performed after a cuffed endotracheal tube

has been inserted. Many units avoid the use of gastric lavage and rest content with gastric decontamination through the use of activated charcoal.

Intake-output charts should be carefully kept, and fluid, electrolyte and acid-base balance should be carefully maintained.

Barbiturate poisoning is an indication for forced diuresis with alkalinization of the urine, in the hope that elimination of the drug is increased via the kidneys. Forced diuresis is more useful in poisoning by long-acting barbiturates which are largely excreted by the kidneys, than in short-acting barbiturates which are mainly metabolized by the liver. We have stopped using forced diuresis with alkalinization of the urine, as cardiorespiratory support with critical care suffices in the successful management of these patients.

Hemodialysis and Hemoperfusion

These procedures in our opinion are rarely necessary. Their chief indication is in patients who are comatose and who are oliguric and in renal failure. They may also be used in patients who are known to have ingested large quantities of sedative-hypnotics, and who have blood phenobarbitone levels close to 100 µg/mL (levels of other barbiturates around 50 µg/mL). We have however found equally satisfactory results in these patients with just cardiorespiratory support and good overall critical care, provided renal function remains adequate.

NARCOTIC POISONING[1-3]

Narcotic poisoning is encountered in patients attempting suicide with narcotics, and perhaps more frequently in addicts as a result of an accidental overdose. Children and elderly patients often show a marked sensitivity to morphine and other narcotics, so that serious toxic effects can occur with average usual doses. Myxedema, adrenocortical insufficiency, chronic liver disease, renal failure, head injuries, and increased intracranial tension from any cause are important medical problems where the use of opium, morphine or heroin can prove disastrous.

The clinical features are characterized by increasing paralysis of the central nervous system with severe involvement of the brainstem. Unconsciousness, with extra selective depression of the respiratory center (causing a very slow respiratory rate that can culminate into apnea), and pin-point pupils, form a triad observed in narcotic poisoning. The diminished tidal volume and slow respiratory rate result in a fall in alveolar ventilation. Hypoxic and hypercapnic respiratory failure result.

Bradycardia, hypotension, hypothermia also occur. Non-cardiogenic pulmonary edema can occur in 50% of the patients, particularly in heroin poisoning.

Organic or structural damage to the brainstem and organophosphorus poisoning can both cause coma and miosis. The intravenous atropine test is of great diagnostic value in organophosphorus poisoning. Organic or structural damage to the brainstem is associated with focal signs and disturbances in cranial nerve function or conjugate gaze. Patients with brainstem lesions are frequently hyper-excitable or have irregular breathing, rather than the slow shallow respiration observed in narcotic poisoning.

In addition to the toxic effect of a narcotic, an addict is exposed to a variety of neurological and infectious complications resulting from the use of crude adulterants (lactose, quinine, etc.), and various infectious agents (due to non-sterile administration). CNS complications from injections of heroin mixtures include toxic amblyopia and acute transverse myelopathy involving the cervical or thoracic cord resulting in paraplegia. Infective complications include sepsis, pyemic abscesses, and bacterial endocarditis most often involving the tricuspid valve, septic thrombophlebitis, Hepatitis B infection and HIV infection. Acute toxic myopathy with myoglobinuria causing renal failure can occur after injections with adulterated heroin.

Management

The principles of management remain unaltered. Cardiorespiratory support, and in particular ventilator support is life-saving.

Specific Antidote

Naloxone is fortunately a specific antidote. Between 0.4–0.8 mg is administered intravenously. When overdose is related to codeine, pentazocine or propoxyphen, a larger dose of 2 mg is given intravenously. Naloxone causes a dramatic improvement in respiration and circulation, the effect on respiration being observed within 2 minutes. It has however no effect on the pupils or on the level of consciousness. The drug has a short half-life and may need to be repeated frequently to reverse the effects of the narcotic on vital centers. If naloxone produces no effect on the shallow, slow respiration, the diagnosis of narcotic poisoning is questionable.

Complications of narcotic poisoning include pneumonia, atelectasis, pulmonary edema, and bacterial endocarditis chiefly involving the tricuspid valve. These need critical care.

OVERDOSE WITH TRICYCLIC ANTIDEPRESSANTS[9-11]

Tricyclic antidepressants such as tryptomer, amitriptyline, doxepin, block uptake of norepinephrine in adrenergic nerves. Toxic effects are due to α-adrenergic blockade, strong anticholinergic activity, inhibition of serotonin and norepinephrine uptake and myocardial depression. As they reduce intestinal motility due to their anticholinergic effect, absorption may be slow and prolonged, increasing the half-life of the drug to 3–4 days.

Clinical Features

Peripheral anticholinergic effects include tachycardia, mydriasis, urinary retention, ileus, dry, hot skin, altered mental state, seizures and occasionally respiratory depression.

Tricyclic antidepressants cause a blockade of the fast sodium channels in the myocardium producing a quinidine like effect. Cardiotoxicity is manifested by prolonged QT, prolonged PR, atrioventricular (AV) block, and tachycardia. Various arrhythmias including ventricular tachycardia, hypotension and impaired myocardial function are observed. Death commonly results from arrhythmias and/or hypotension.

Convulsions are commonly observed in TCA poisoning and in association with diminished sweating can cause life-threatening hyperpyrexia.

Diagnosis

A combination of anticholinergic effects and cardiovascular abnormalities should suggest the diagnosis. Tachycardia, prolonged PR interval and a prolonged QT interval on the ECG are commonly seen. The QRS interval is prolonged in patients with marked overdose; the mean QRS axis in the frontal plane is often upward and to the right, causing a prominent R in avR and a prominent S in lead I and avF.

Drugs levels are not necessary to make a clinical diagnosis of acute poisoning.

Management[10,11]

- Emergency management should concentrate on ensuring a secure airway, breathing and restoring hemodynamic stability. Seizures if present need quick control. Activated charcoal may be used if there are no contraindications.
- *Bicarbonate therapy* IV sodium bicarbonate is the antidote for cardiotoxicity. It can reverse hypotension, cardiac arrhythmias, AV conduction abnormalities and should be given when the QT interval is prolonged (>100 msec). The drug should also be given in the presence of acidosis (pH <7.20). The drug is given as an initial bolus of 1–2 mEq per kg followed by an infusion of 150 mEq in one liter of 5% dextrose at the rate of 2–3 mL/kg per hour. The target aimed at is an arterial pH of 7.45–7.50.

The benefits of sodium bicarbonate are in part related to the action of sodium on the conductivity of the sodium channels in the myocardium. Hypertonic saline has been used in refractory cases to restore conductivity in the sodium channels of the myocardium.

If arrhythmias continue in spite of IV sodium bicarbonate, anti-arrhythmic drugs may be necessary. Type Ia and Ic anti-arrhythmic like procainamide and flecainide should be avoided in the management of arrhythmias. Lidocaine has not been shown to be of use in VT caused by TCA. Magnesium sulfate is perhaps the drug of choice in wide complex tachycardia unresponsive to other drugs.

Hemodialysis or hemoperfusion are not beneficial in TCA poisoning as these drugs are strongly protein bound. Physostigmine should not be used to counter the anticholinergic effects of TCA because of the toxic effects this drug can cause.

COCAINE POISONING[12-14]

Cocaine addicts are on the increase. The drug can be sniffed, taken orally, injected intravenously, and can be smoked in a free base form, or mixed with baking soda and water and smoked as the "crack" form. Absorption from all sites is rapid.

Clinical Effects

Cocaine poisoning results in a sympathomimetic toxidrome. Mechanisms of action are enhanced catecholamine release with a marked increase in circulating catecholamines, inhibition of monoamine uptake and a blockade of sodium channel activity. Cocaine poisoning is typically characterized by life-threatening cardiovascular, CNS and pulmonary complications.

Cardiovascular effects are most prominent. These include hypertension and arrhythmias. Hypertension may be severe enough to cause intracranial bleeding or an aortic dissection. Both supraventricular and ventricular arrhythmias may occur. Myocarditis has followed cocaine use; this is associated with gross ST-T changes on the ECG, and a rise in the CK-MB fraction. Cocaine is a vasoconstrictor, and this may result in organ ischemia. Myocardial infarction, bowel infarction, renal infarction and ischemia involving a limb, have all been noted to occur.

The CNS manifestations of cocaine are important, they may be the presenting feature. These include seizures, cerebral infarction, subarachnoid and intracerebral hemorrhage. Intracerebral aneurysms and arteriovenous malformations are frequent on angiographic examination. Overdosage of cocaine, even in addicts, can lead to severe mental obtundation and coma. Cocaine abuse should always be considered in the differential diagnosis of a stroke in young patients. Strokes may occur 24 hours after the use of cocaine. Though commoner in chronic cocaine use, they may also occur after the drug is used for the first time.

Severe cocaine intoxication can cause non-cardiogenic pulmonary edema. Rhabdomyolysis and hyperthermia may occur with excessive muscle activity, particularly in those presenting with repeated seizures. Investigations should include an ECG, X-ray chest, creatine kinase (CK) estimation, urine for myoglobin. Relevant imaging studies of the head are necessary when CNS manifestations, in particular a neurologic focal deficit is observed. A toxicological screen for cocaine is asked for, to help diagnosis.

Diagnosis

Urine may test positive for cocaine for 2–3 days after ingestion; false negative results have also been observed.

Differential Diagnosis

Overdose of sympathomimetic drugs, (in particular amphetamine), anticholenergic drugs, theophylline can produce a similar picture. Cocaine intoxication could be confused with CNS infections. Cocaine overdose, as stated earlier, should

always enter into differential diagnosis of the etiology of a stroke, particularly in young patients.

Management[13,14]

Supportive measures include the use of activated charcoal in those who have ingested the drug. Cardiorespiratory support is essential in acute severe overdosage.

Benzodiazepines and antihypertensives (other than beta-blockers) form the corner-stones of therapy. Diazepam 5–10 mg is given at 5–10 minute intervals and serves to control agitation and other manifestations of toxicity. Symptomatic treatment should be offered with regard to cardiovascular, CNS and pulmonary complications.

Seizures should be controlled with IV diazepam or lorazepam. If uncontrolled and very frequent, the patient is paralyzed with a neuroparalytic drug, and kept on ventilator support.

Hypertension requires sedation and the use of antihypertensive drugs. Acute crisis may necessitate a titrated infusion of sodium nitroprusside. Calcium channel blockers and pentaloamine can also be used. Beta-blockers should not be given as unopposed α-adrenergic activity could worsen hypertension and cause coronary vasoconstriction.

Supraventricular arrhythmias are treated by calcium channel blockers. Pure beta-blockers should be avoided. Ventricular arrhythmias are best treated with IV lidocaine. Oxygen, use of benzodiazepine must always be given and any disturbance in electrolyte balance corrected. Myocardial ischemia can trigger arrhythmias; IV nitroglycerin helps to correct myocardial ischemia. Class Ia anti-arrhythmic drugs (procainamide) should be avoided.

Hyperthermia

Increase in body temperature may be marked in patients having repeated seizures. Treatment includes the use of sedatives and external methods of cooling.

Rhabdomyolysis

Rhabdomyolysis when present, is treated with intravenous fluids and alkalinization.

See Table 6 for drugs contraindicated in cocaine poisoning.

Table 6: Contraindicated drugs in cocaine poisoning

Beta-blockers	Contraindicated because of unopposed ∝-adrenergic action
Class Ia anti-arrhythmic—procainamide	May increase QT interval; worsen arrhythmia
Phenothiazines an antipsychotic drugs	Increased seizure risk Increased dystomic movement Increased QT interval
Succinylcholine	Can exacerbate rhabdomyolysis, induce hyperkalemia

ORGANOPHOSPHORUS OR INSECTICIDE POISONING[15-17]

Organophosphates are found in insecticides and herbicides. Drinking organophosphorus compounds (chiefly TIK 20 or Parathion) with suicidal intent has been for the last 40 years, the commonest form of poisoning in the lower socioeconomic strata of society in this country. Organophosphates act by causing irreversible inactivation of acetylcholinesterase. This results in the accumulation of acetylcholine at cholinergic receptors. Excess acetylcholine has muscarinic effects, nicotinic effects and toxic effects on the central nervous system.

Organophosphorus poisoning can occur from accidental ingestion of an insecticide, as also due to accidental dermal exposure. Inhalation via the lungs can also cause poisoning. Food, including stored grain contaminated by a spray of these insecticides has also been known to lead to severe toxicity.

Clinical Features

Organophosphorus poisoning results in a cholinergic "toxidrome". Peripheral muscarinic effects include bronchospasm, vomiting, diarrhea, miosis, blurred vision, salivation, diaphoresis, lacrimation and urinary incontinence. Tachypnea with severe respiratory distress is observed in many patients.

Nicotinic effects are chiefly observed in skeletal muscles; fasciculation, weakness and even paralysis can occur.

Patients may have bradycardia or tachycardia and may be hypertensive or hypotensive, depending on whether the muscarinic or nicotinic effects predominate.

Excess of acetylcholine also has a toxic effect on the CNS. Confusion, seizures and ultimately coma result. The terminal picture is one of flaccid paralysis, respiratory cum peripheral circulatory failure, pulmonary edema and deep coma. Respiratory failure is related to a combination of central depression, muscle weakness, bronchospasm and pulmonary edema. Severe organophosphorous poisoning is characterized by multiple organ dysfunction and failure, the organs chiefly involved being the lungs, the cardiovascular system, the central nervous system and the renal system. High SOFA scores (>10) are observed in some of these critically ill patients.

An "intermediate syndrome" may occur 1–4 days after an apparently well-treated cholinergic crisis. Its main clinical features are sudden respiratory paralysis, cranial motor nerve palsies, neck flexor muscle and proximal limb muscle weakness and paralysis. It has been documented for fenthion, diazinon, malathion, trichlorfon, dimethoate and sumithion. Treatment is by providing respiratory support; atropine and pralidoxime are ineffective. Recovery begins 5–15 days after onset of weakness.

In some patients brought in a comatose state, increased motor tone resembling decorticate or decerebrate rigidity may be observed.

Diagnosis

Coma with pinpoint pupils should bring to mind the possibility of organophosphorus poisoning. There is often a characteristic garlic odor to the breath. This diagnosis can be proved by estimating cholinesterase levels in the blood. Levels below 50% of normal indicate intoxication. Treatment in suspected poisoning should be immediate.

Management[17,18]

Activated charcoal should be administered, if the patient is brought within few hours of the ingestion of the poison.

Intravenous atropine is both of diagnostic and therapeutic value. A patient brought into a unit nearly dead with respiratory paralysis, coma, pulmonary edema following organophosphorus poisoning can still be resuscitated with prompt use of atropine and good cardiorespiratory support.

A 2 mg dose of atropine is given slowly intravenously every 5 minutes till the pupils start to dilate. As much as 50–100 mg may need to be used in some patients. Once the pupils dilate to a normal size, atropine is stopped; if over a period of hours the pupils again constrict, further atropine is necessary. The continued use of atropine after the pupils have returned to normal size, can lead to atropine intoxication. Atropine antagonizes the muscarinic effect of excess acetylcholine and reduces the effect of the poison on the CNS. It has no action on the nicotinic effects on skeletal muscles, nor does it restore acetylcholinesterase.

Atropine has also no effect on respiratory paralysis. Ventilator support is necessary. PEEP may be used in the presence of pulmonary edema, once the circulation and the blood pressure have stabilized.

Pralidoxime restores cholinesterase activity. The drug reverses the nicotinic effects of muscle weakness, and also reverses some of the CNS effects. It is used in conjunction with atropine. The dose of pralidoxime is 0.5–2 g (25–50 mg/kg), given intravenously over 5–15 minutes. Increased muscle strength and control of fasciculations are generally observed in 15–60 minutes. The drug can be repeated in 1–2 hours if muscle weakness and fasciculations persist or recur. Further doses of pralidoxime can be given every 6–12 hours, if necessary.

In severe poisoning atropine and pralidoxime may need to be given for several days. The drugs are discontinued when clinical improvement is persistent and satisfactory, and when clinical features of toxicity do not recur on withholding the drugs.

In many hospitals in the country, pralidoxime is not easily available. In its absence fresh blood transfusions should be tried.

Cardiorespiratory support is vital for survival. Early intubation, ventilator support (if necessary with PEEP) and inotropic support with dobutamine, dopamine, and vasopressor support with norepinephrine are all necessary in hypotensive patients with respiratory failure. Support to all other organ systems is important as organophosphorous poisoning leads to multiple organ dysfunction and failure.

Charcoal hemoperfusion significantly increases the clearance of organophosphorus compounds and is indicated in severe poisoning.

Seizures may need symptomatic control with diazepam (10–20 mg intravenously) and by phenytoin sodium.

ANTIHYPERTENSIVES

Beta-Blockers[19,20]

Beta-blockers are among the most frequently used drugs in hypertensive patients. Patients may take a larger dose than that prescribed, by sheer accident, and manifest signs of drug toxicity. Life-threatening toxicity may occur even if the dose taken is two or three times over the therapeutic range. Toxicity has also been observed with ocular preparations. Rarely beta-blockers are consumed in large doses with suicidal intent. Toxicity generally occurs within 6–8 hours. Ingestion of extended release preparations and sotalol may be associated with delayed toxicity, necessitating observation for 24–48 hours.

Clinical findings of beta-blocker toxicity are hypotension, bradycardia and AV conduction abnormalities. The latter may take the form of first, second or third degree AV block. SA block is also observed and the QRS interval is often prolonged. In severe poisoning, the blood pressure is unrecordable, the cardiac output very low due to the depressant action of the drug on the myocardium, and the patient goes into cardiogenic shock. Death is due to asystole.

The more lipophilic beta-blockers, like propranolol, metoprolol, timolol for unclear reasons, can cause CNS dysfunction in the form of delirium, seizures and coma, even in the absence of significant hypotension. Hypoglycemia and hyperkalemia may also be observed. Overwhelming life-threatening bronchospasm may occur in patients with asthma or chronic obstructive pulmonary disease (COPD).

Treatment

Patients who present within 2–4 hours after ingestion should be given activated charcoal, the dose of which can be repeated. Patients who appear stable should be closely monitored for 24–48 hours.

Bradycardia and hypotension are initially treated with intravenous atropine and a volume load with isotonic saline. If bradycardia and hypotension persist, the specific drug to use is glucagons 5 mg intravenously; the dose can be increased to 10 mg if the response is poor. If a response to glucagons is satisfactory, the drug is given in an intravenous infusion at the rate of 10 mg/hour. Bronchospasm is treated by nebulization with duolin, budecort and by IV hydrocortisone.

Calcium chloride 10% may be given intravenously slowly up to a maximum of 3 g. This improves cardiac contractility and helps to reverse hypotension.

Catecholamine infusions should also be started if hypotension is severe and persistent. Very often a combination of dopamine, dobutamine and epinephrine or norepinephrine is used; the response is often poor, so that very large doses may be necessary to produce a satisfactory effect. The danger of tachyarrhythmias due to large doses of inotropes should be kept in mind. External or transvenous pacing should be considered early in the presence of a marked bradyrhythm. Pacing may increase the heart rate without increasing blood pressure or cardiac output. At times the pacemaker fails to capture. Phosphodiesterase inhibitors such as milrinone may prove useful in patients with cardiogenic shock.

Beta-blockers have very large volumes of distribution and cannot be effectively cleared by extracorporeal methods. Atenolol, sotalol and acetabutol are exceptions that can be eliminated by extracorporeal methods in case of severe toxicity, particularly in patients with renal failure.

Calcium Channel Blockers[21]

Calcium channel blockers are also frequently used in the management of hypertension. The most commonly used calcium channel blockers are verapamil, diltiazem and nifedipine. These drugs are well absorbed from the gastrointestinal tract; they are metabolized in the liver.

Calcium channel blockers in an overdose have a marked negative inotropic effect on the heart and induce severe peripheral vasodilatation. Patients present with bradycardia, hypotension and various degrees of heart block that may result in death. Toxic effects outside the cardiovascular system include nausea, vomiting, non-cardiogenic pulmonary edema, mental changes, hyperglycemia and seizures.

Treatment

Calcium is administered intravenously. More often than not the result is unsatisfactory, as the calcium channels are blocked, so that additional calcium has little or no effect. Even so, calcium is administered as 10 mL of 10% $CaCl_2$ given over 2–3 minutes; additional doses are given every 2–3 minutes and if hemodynamic instability persists a continuous infusion of 10% $CaCl_2$ at 10 mL/hour is administered.

Glucagon and phosphodiesterase inhibitors should be used in the manner outlined for beta-blocker overdose. Glucose insulin infusion (keeping the blood sugar between 150–200 mg/dL) may help in patients who do not respond to the above measures. Atropine, 1 mg intravenously can be used to increase the heart rate in some patients. Hypotension should be further combated by a volume load and by catecholamine infusions. As in the treatment of beta-blocker overdose, a combination of dopamine, dobutamine, and epinephrine or norepinephrine may be necessary. Transvenous pacing should be done in patients with severe heart block.

SYMPATHOMIMETIC DRUG OVERDOSE[22]

Sympathomimetic drugs like amphetamine and methamphetamine are very popular drugs of abuse. However, sympathomimetic drugs are also present in over the counter preparations for colds, for appetite control, and include stimulants such as caffeine, ephedrine and pseudoephedrine.

These drugs (amphetamine and methamphetamine are classic examples) in an overdose, cause an excessive release of catecholamines, epinephrine and norepinephrine, resulting in a sympathomimetic toxidrome. The latter is characterized by tachycardia, hypertension, agitation, restlessness, anxiety and mydriasis. Hallucinations, acute and often paranoid psychosis and seizures may occur. The psychosis is indistinguishable from that observed in schizophrenia. It is temporary, but may take weeks or even months to disappear.

Other cardiovascular and CNS effects observed with severe overdose include myocardial ischemia, arrhythmias, strokes, intracranial hemorrhage. Hyperthermia, rhabdomyolysis, renal failure and diarrhea may also occur.

Methamphetamine is more frequently used than amphetamine as a drug of abuse. It is termed "ice" or "crank"; the drug can be ingested, smoked, inhaled or given intravenously. Another amphetamine-like drug increasingly used not only in the West but also in India and many countries of the world is 3–4 methylenedroxymethamphetamine. It is popularly called "Ecstasy" and acts both as a stimulant and hallucinogen. It produces the serotonin syndrome by inducing a release of serotonin in the brain and inhibiting its re-uptake. Besides its hallucinogenic and stimulant effect, the drug induces continuous physical activity. Complications include hyperthermia, rhabdomyolysis, circulatory collapse, strokes, intracranial hemorrhage and multiple organ dysfunction syndrome.

Diagnosis

When no history is available the sympathomimetic toxic syndrome should be distinguished form thyrotoxicosis, alcohol or benzodiazepine withdrawal, from poisoning caused by tricyclic antidepressants, and from symptoms induced by the interaction of monoamine inhibitors with other drugs.

Treatment

Treatment is directed to countering the cardiovascular system and CNS effects. Acute hypertension is an emergency that should be promptly controlled. A titrated solution of sodium nitroprusside given in an intravenous infusion is the quickest method to control a sharp rise in the blood pressure. Labetalol is a good choice in patients who have marked tachycardia and hypertension. Other beta-blockers should be avoided as increasingly severe hypertension could result from beta 2 adrenergic block and unopposed α-adrenergic stimulation.

Anti-arrhythmics like verapamil or adenosine are used to revert supraventricular arrhythmias.

Seizures should be treated with benzodiazepines, phenytoin and phenobarbitol. Benzodiazepines are probably the drugs of choice in the management of psychosis. Hyperthermia can be lethal. Abolishing seizures and restlessness with benzodiazepine and physical cooling of the skin by appropriate methods are important.

Myocardial ischemia requires close ECG monitoring and serial cardiac enzyme estimation. Tachycardia should be controlled; nitrates either orally or as an intravenous infusion of nitroglycerine should be administered for the treatment of myocardial ischemia.

ASPIRIN (SALICYLATE) POISONING[23]

Aspirin is one of the most commonly and widely used drugs today. Remarkably enough, poisoning with aspirin is rarely encountered in our country. The drug is available and sold over the counter as an aspirin preparation *per se*, or in combination with other drugs. Methyl salicylate (Oil of Wintergreen) poisoning occurs at times in children who ingest it because of its pleasant smell. This formulation contains as much as 7 g of aspirin per teaspoon, compared to the usual 300–600 mg aspirin per tablet in the usual aspirin preparations.

Aspirin after oral ingestion, reaches a peak level in the blood after 2 hours. It is metabolized in the liver, is also excreted by the kidneys and has a half-life of 4–6 hours. When an overdose is taken, the hepatic enzymes become saturated and the drug's half-life increases to 18–36 hours. The drug can now only be eliminated via the kidneys. When blood levels are high (>40–50 mg/dL), serious toxic effects can occur.

It is best to consider patients with aspirin or salicylate poisoning as falling into two groups, those who ingest the drug with suicidal intent, and those who take the drug on a long-term basis to counter pain. Overdose with aspirin in the latter group can have subtle manifestations which are easily missed and which contribute significantly to morbidity and mortality.

Clinical Features

Tinnitus, vertigo, vomiting and impairment of hearing are frequent. Mental confusion, restlessness, excitability may resemble alcoholic intoxication. Sweating, dehydration and hypotension are often observed. In severe cases hallucinations, seizures, coma and death occur.

Salicylates initially stimulate the respiratory center and induce hyperventilation with a respiratory alkalosis. They also directly cause a metabolic acidosis with an increase in the anion gap. Thus a combination of respiratory alkalosis with metabolic acidosis should strongly suggest the possibility of salicylate or aspirin poisoning. In children, or following large doses in adults, there can be a depression of the respiratory center so that a combination of respiratory plus metabolic acidosis results, with a life-threatening fall in the arterial blood pH.

Large doses produce hemorrhage due to hypoprothombinemia. Hematemesis and malena may result from acute erosive gastritis and duodenitis. Cerebral edema can occur and non-cardiogenic pulmonary edema results from increased capillary permeability. Salicylates uncouple the phosphoregulation process; this lead to increased glucose utilization, an increased metabolic rate and increased oxygen consumption. The clinical effects of the above are hypoglycemia and fever.

It is extremely important to note that features of hyperventilation, seizures, dehydration and even coma, can occur in patients with chronic poisoning, even when salicylate levels are not inordinately high (35–50 mg/dL).

Diagnosis

The diagnosis may be difficult in the absence of a relevant history. Chronic overdose in patients is very easily missed.

The occurrence of metabolic acidosis and respiratory alkalosis, in the absence of diabetes and renal failure should suggest the possibility of salicylate poisoning. The diagnosis can be proved by measuring salicylate levels in blood. This can be done at the bedside by doing the Phensitix test which detects salicylates in the plasma if the level is more than 20 mg/dL.

Common laboratory findings in salicylism include an elevated anion gap metabolic acidosis, increased prothrombin time, hypernatremia, hypo- or hyperglycemia, ketonemia, hypokalemia, and increased levels of liver transaminases.

The differential diagnosis is from poisoning by CNS stimulants which can also cause an altered mental state, confusion, and diaphoresis. Alcoholic ketoacidosis and other causes of metabolic acidosis need to be distinguished from salicylate poisoning. Encephalitis may present with hyperventilation, mental confusion and respiratory alkalosis. Sepsis can also be characterized by respiratory alkalosis or a combination of respiratory alkalosis plus metabolic acidosis.

Management

The repeated use of activated charcoal is helpful if the patient presents within 2–3 hours after ingestion of the drug.

Correction of dehydration and shock, and efficient cardiorespiratory support are of prime importance. Maintenance of electrolyte and acid-base balance is crucial for survival in severe poisoning. Severe metabolic acidosis should be promptly corrected with 75–150 mL of intravenous sodium bicarbonate (see Chapter Acid-Base Disturbances in the Critically Ill).

Use of forced diuresis with alkalinization of the urine In an alkaline medium, salicylates remain in the ionized form and do not diffuse into the tissues. Alkalinizing the urine facilitates excretion of salicylates. One should aim to maintain a urine pH of 7.5–8. Salicylism is one poisoning where forced diuresis with alkalinization should as far as possible be attempted. The simplest method of alkalinization is to use 1 L of half strength (0.45%) saline, to which is added two ampoules of 7.5% sodium bicarbonate and infuse this at the rate of 150–250 mL/hour. Potassium deficits are appropriately replaced. Intravenous mannitol 300 mL, as also furosemide 40 mg intravenously may be administered to increase diuresis. The intake should continue to keep pace with the output, and it is important to check serum electrolytes frequently so that electrolyte balance is well maintained. Hypernatremia, cerebral and pulmonary edema are complications that need to be carefully watched for.

Box 1: Indications for hemodialysis or hemoperfusion in salicylate (aspirin) poisoning

- Severe acid base disturbance
- Renal failure, hepatic dysfunction
- ARDS/ALI
- Severe refractory hemodynamic instability
- CNS features: Coma, seizures
- Serum salicylate levels >120 mg/dL for acute poisoning
- Serum salicylate levels >60 mg/dL for chronic toxicity

Hemodialysis and Hemoperfusion

These very effectively reduce salicylate levels in blood and are indicated under the following circumstances—

- Serum levels greater than 120 mg/dL in acute poisonings observed within 6 hours of ingestion, or greater than100 mg/dL if observed after 6 hours of ingestion of the poison.
- Chronic toxicity when blood level exceeds 60 mg/dL.
- In patients with renal failure and/or hepatic dysfunction.
- In the presence of pulmonary edema which prevents the use of forced diuresis and alkalinization.
- Progressive hemodynamic deterioration.
- In the presence of severe neurological toxicity, coma or seizures.
- In the presence of clinical deterioration in spite of conservative conventional management.

Indications for hemodialysis or hemoperfusion in salicylate (aspirin) poisoning are listed in Box 1.

Symptomatic Measures

Seizures may need the use of diazepam; blood transfusions may be necessary to replace blood lost in hematemesis. Vitamin K should be given to counter hypoprothrombinemia. Hypovolemia should be treated by fluid infusions. Non-cardiogenic pulmonary edema can result from the effect of salicylates on pulmonary capillaries. Intubation and ventilator support then become necessary.

PARACETAMOL (ACETAMINOPHEN) POISONING[24]

Paracetamol is an antipyretic and analgesic very frequently used in medical practice. Overdose with suicidal intent is one of the commonest poisonings in the West, but is uncommon in our country. Patients may suffer poisoning from the drug by inadvertently consuming excessive quantities in an attempt to treat their own pain and fever. It is important to bear in mind the fact that paracetamol is often present in combination with other drugs bearing different brand names.

The drug after ingestion is metabolized in the liver via the cytochrome P 450 oxidase system. Excessive quantities of paracetamol deplete glutathione stores. This leads to accumulation of toxic metabolites that are severely hepatotoxic and can result in massive hepatic necrosis. In adults doses of less than 125 mg/kg are rarely toxic except when patients have pre-existing liver disease. Acute ingestion of 150 mg/kg (10 g) or chronic ingestion of 4 g/day results in clinical toxicity. Ingestion over 200–250 mg/kg invariably leads to fulminant hepatic failure. Death occurs within 4–15 days after ingestion of the drug in these patients.

Clinical Features

Patients with an overdose of paracetamol are minimally symptomatic in the first 24 hours. Sweating, nausea, vomiting may be observed. Hepatotoxicity starts after 24–48 hours and usually reaches a maximum between 72–96 hours. It is characterized by deepening jaundice, mental confusion and asterixis. Drowsiness progresses to coma; hypoglycemia and excessive bleeding are observed. Death occurs from acute hepatic failure. The serum transaminases and bilirubin show a progressive rise *pari passu* with the clinical deterioration. The prothrombin time is markedly elevated and the serum ammonia levels are high.

Acute tubular necrosis with renal failure can also occur. Pancreatitis, myocardial dysfunction and hypersensitivity reactions have been reported.

Laboratory Investigations

The most important test is the serum acetaminophen level. It should be done 4 hours after ingestion of the drug. If this is over 150 µg/mL, the patient is at risk for massive hepatic necrosis and should be promptly treated with N-acetylcysteine.

In patients admitted later than 4 hours after ingestion, the paracetamol level should be plotted against time using the Rumack-Matthew nomogram. Plasma levels above the lower line "possible risk" should be given N-acetylcysteine (NAC). The administration of NAC should not be delayed in a witnessed poisoning. NAC should also be administered in patients who come after 24 hours of ingestion if there is a rise in liver enzymes or if there is a detectable acetaminophen level in the blood.

Liver function tests need to be done and followed-up at periodic intervals in patients who show hepatotoxicity.

Management

Activated charcoal should be given if the time lag between ingestion of the poison and admission to a unit is less than 6 hours. Activated charcoal also absorbs the antidote N-acetylcysteine, but the dose of the latter can be suitably increased. The use of activated charcoal is not likely to help in late admission to hospital or to a critical care unit.

Use of N-acetylcysteine The antidote is indicated: (a) in patients who have consumed excess quantities of the drug; (b) in those with toxic serum levels as indicated earlier; (c) in those showing evidence of impaired hepatic function.

The drug is most effective when given within the first 8 hours of ingestion. After this period, its efficacy decreases, but it should nevertheless be given. There is no benefit in giving acetylcysteine in the first 4 hours after ingestion. The

drug acts by increasing depleted glutathione stores, and by providing a glutathione substitute to allow for degradation and detoxification of metabolites of paracetamol within the liver.

N-acetylcysteine is usually given orally in a loading dose of 140 mg/kg followed by 70 mg/kg every 4 hours for 3 days. This antidote may unfortunately cause vomiting. Prochlorperazine or metoclopramide may be used to counter the latter. The drug can also be used intravenously in the same dose as stated above in patients where severe vomiting precludes oral use. It is best given in 500 mL of a diluent over a period of 2 hours.

Supportive care for liver cell failure is important. This has been discussed in another chapter. The indications for liver transplant in severe paracetamol poisoning have been discussed in the Section Critical Care in Acute Hepatic Failure to which the reader is referred.

CARBON MONOXIDE POISONING[25]

Carbon monoxide (CO) has a 200 times greater affinity for hemoglobin compared to oxygen. It therefore readily displaces oxygen from oxyhemoglobin (HbO_2), which is converted to carboxyhemoglobin (HbCO). Severe tissue hypoxia results and this can cause death. An exposure concentration of 0.4% of CO is fatal within an hour. CO is solely eliminated via the lungs, the time taken to reach half the original concentration being about 4 hours breathing air, and about 80 minutes breathing 100% oxygen.

Clinical Features

Tissue hypoxia results in a loss of consciousness followed by respiratory failure. Circulation may continue for some minutes after respiration has failed. There is a cherry pink color to the skin, nails and mucosa.

Diagnosis

This is generally obvious from the circumstances in which a patient is found. At times CO poisoning is insidious. A slow gas leak may not be evident, and the diagnosis in a patient found unconscious in such circumstances is easily missed. A diagnosis of a brainstem infarct is erroneously made. Hypoxia produces lactic acid acidosis and a common finding is low arterial blood pH, a normal PaO_2 with lactic acid acidosis. Low oxygen saturation in the presence of a normal or near normal PaO_2, should promptly arouse suspicion of CO poisoning or methemoglobinemia.

For the estimation of CO, 3 mL of heparinized blood is collected under liquid paraffin, and sent to the laboratory. Spectroscopic examination of the blood reveals the typical band of carboxyhemoglobin (HbCO), and confirms the clinical diagnosis. A rough but simple bedside test for carboxyhemoglobin is as follows, 1 mL of patient's blood is added to 10 mL distilled water plus 1 mL of 5% NaOH. Carboxyhemoglobin is present if the solution turns straw yellow (HbCO <20%), or remains pink (HbCO >20%). An HbO_2 solution turns brown.

Management

Emergency management consists of immediate cardiorespiratory support. The patient is quickly intubated and put on ventilator support with 100% oxygen. When facilities are available, hyperbaric oxygen at 2 atmospheres pressure rapidly produces dissociation of CO from hemoglobin, and this promptly corrects tissue hypoxia. Hyperbaric oxygen if available, can help resuscitate even moribund patients.

If resuscitation from CO poisoning is delayed, serious neurological sequele can result even after complete recovery of consciousness.

CYANIDE POISONING[26]

Cyanide is the quickest acting poison. It affects the cytochrome oxidase system within the cells thus preventing the latter from utilizing oxygen. Strangulation literally occurs at the cellular level. Death occurs within a few minutes following inhalation or ingestion. Oral ingestion of hydrocyanic acid acts more slowly, death occurring within an hour. An odor of bitter almonds and the sudden catastrophic episode, point to the diagnosis.

Clinical features include coma, rigidity, respiratory depression, bradycardia and hypotension. A patient brought alive to the ICU immediately after ingestion of cyanide showed deep coma, marked bradycardia, hypotension, absent brainstem reflexes, severe rigidity and extensor thrusts as in a decerebrate state. Plantars were unelicitable. A diagnosis of a brainstem infarct or hemorrhage was entertained. The correct diagnosis was made retrospectively after the patient miraculously recovered just on cardiorespiratory support after a period of 10 hours. He confessed to ingesting a powder, which on analysis contained cyanide.

Management

Immediate inhalation of amyl nitrite pearls (one every 2 minutes), should be followed by an intravenous injection of 10–15 mL of 3% solution of sodium nitrate given over 5 minutes. The above measures produce a methemoglobinemia, and the cyanide is bound as stable cyanmethemoglobin.

The next step is the administration of 50 mL of a 25% solution of sodium thiosulfate. This helps conversion of cyanide liberated from cyanmethemoglobin to thiocyanate.

Cyanide is rapidly destroyed in the body, so that if the patient can be tided over a period of a few hours, recovery may well occur.

ALCOHOLS[27]

All alcohols have a depressant effect on the CNS. Dysarthria, lack of co-ordination, altered often aggressive behavior, increasing drowsiness progressing to deep coma are observed. Respiratory depression and failure together with the characteristic alcohol odor in the breath allow a correct diagnosis.

Ethanol

The diagnosis of ethanol poisoning can be made from the above clinical features and confirmed by measuring the blood ethanol level. Treatment is largely supportive. In obtunded patients, the airway should be secured; mechanical ventilator support is essential in the presence of respiratory complications. It is important to remember that in an unconscious patient with the breath smelling of alcohol and with a raised ethanol level in blood, the unconsciousness is not necessarily related to alcohol. The unconsciousness may well be due to a subdural hematoma (related to a fall or injury) during a drunken state or to a coincident cerebrovascular accident.

The three non-ethanol toxic alcohols that on ingestion can cause life-threatening emergencies and death if not diagnosed promptly, are methanol, ethylene glycol and isopropanol.

Methanol

Poisoning occurs through ingestion of methylated spirit due to suicidal intent or as a substitute for ethyl alcohol. Adulteration of ethyl alcohol with methanol is very common in what is termed in India as country liquor.

Clinical Features

Toxic effects may occur after a latent period of 12–48 hours. Major toxicity of methanol is related to the oxidation of methanol to methanal, formic acid and finally detoxified to carbon dioxide. Toxic manifestations consist of increasingly severe metabolic acidosis, blurred vision progressing to blindness due to optic atrophy, seizures, respiratory failure, coma and death. There is an increase in both the anion gap and the osmolar gap. Epigastric pain, vomiting and other features of alcoholic intoxication as observed with ethanol poisoning often occur to start with. These are followed or accompanied by the more serious toxic effects mentioned above.

Laboratory Investigations

Metabolic acidosis with an increase in the anion gap is always present. An osmolar gap is also a characteristic feature. Definitive diagnosis can be made by measuring methanol levels in blood. However, late presentations of poisoned patient may have undetectable methanol levels but raised formate levels.

Management

Counter acidosis Intravenous sodium bicarbonate is administered to counter severe acidosis. Large amounts may need to be given because toxic acid metabolites are produced in large quantities. Hypernatremia may result from large doses of sodium bicarbonate.

Block or reduce toxic metabolites This is achieved by the administration of ethanol orally or intravenously. The dose of ethanol in an adult is 2 mL/kg of 50% ethanol orally or 10% ethanol intravenously. Ethanol infusions if given intravenously should be at the rate of 0.05–0.1 mg/kg per hour to provide ethanol levels of 100–150 mg/dL. Alcohol dehydrogenase which metabolizes methanol has a higher affinity for ethyl alcohol, and preferentially metabolizes the latter. The methanol therefore remains unmetabolized with less resulting toxic effects.

When available, fomepizole is generally preferred to ethanol as a competitive inhibitor of alcohol dehydrogenase in patients who have methanol levels greater than 20 mg/dL, well marked metabolic acidosis and a large anion and osmolar gap. The drug is given in a dose of 15 mg/kg IV over 30 minutes, followed by 15 mg/kg every 12 hours as needed till methanol levels fall less than 20 mg/dL. Folic acid should be given 50 mg IV every 6 hours to convert the formate to CO_2 and water.

Methanol when taken in a large dose kills quickly and treatment should begin promptly on suspicion of the diagnosis without awaiting results of methanol levels in blood.

Hemodialysis In seriously ill patients, after the above measures are instituted, hemodialysis is used to remove both methanol and its toxic metabolites from the blood.

Ethylene Glycol

Ethylene glycol is present in anti-freeze and is consumed with suicidal intent. Toxicity is related to the formation of toxic metabolites, glycolaldehyde and oxalates because of the action of alcohol dehydrogenase on ethylene glycol. Early toxicity consists of CNS depression. This is followed after a latent period of 5–72 hours by severe metabolic acidosis, renal failure, convulsions, mental obtundation progressing to coma. The urine may fluoresce under wood light and show oxalate crystals. Metabolic acidosis, anion gap, osmolar gap occur quickly. Fomepizole should be used in the dose mentioned above. Hemodialysis is indicated with blood levels of ethyelene glycol greater than 30 mg/dL, severe metabolic acidosis, or renal failure. Seizures are common and treated with benzodiazepines and by IV calcium gluconate if hypocalcemia is present.

Isopropanol

Isopropanol is a component of rubbing alcohol and a few other household compounds, and may be ingested with suicidal intent. It causes epigastric pain, vomiting, GI bleeding, depression of the CNS, ketosis and respiratory failure. The breath has a fruity odor of ketones. Diagnosis is made from the above symptoms and by the presence of unexplained ketosis or an elevated serum osmolar gap.

Treatment is largely supportive as in ethanol poisoning. Hypoglycemia may contribute to a confused obtunded state and should be treated with IV glucose. GI toxic manifestations require use of proton pump inhibitors; GI bleeding necessitates volume replacement and RBC infusions if necessary.

Hemodialysis can successfully remove isopropanol in patients with severe poisoning.

FERROUS SULFATE (IRON) POISONING[28]

Soluble iron when ingested in a marked overdose produces intense vomiting, circulatory collapse, and at times even perforation of the stomach. Jaundice, metabolic acidosis, coma and respiratory failure are observed.

The specific antidote is deferoxamine mesylate (Desferal). This antidote combines with iron to form a harmless compound which is excreted in the urine. After a gastric lavage with 10% sodium bicarbonate, 5–7 g of desferal in 100–200 mL of water is given orally. 2 g of desferal in 6 mL distilled water is given intramuscularly, and the drug is then given in a slow intravenous drip at the rate of 7–10 mg/kg per hour. The maximum dose should not exceed 80 mg/kg in 24 hours. Hemodialysis is effective in severe poisoning.

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CHAPTER 67

Envenomation

GENERAL CONSIDERATIONS

Snake bite is an important yet neglected public health issue and hazard in tropical countries. An accurate measure of the global burden of snake bite envenomation is unknown. There are also no reliable figures with regard to morbidity and mortality following snake bites from countries where snake bite is a frequent and an important problem. South Asia is by far the most affected region and India has the largest number of deaths due to snake bite in the world.[1] The World Health Organization has reported that 50,000 people die of snake bite in India. In Pakistan, 40,000 bites are reported annually with 8,900 fatalities; Nepal and Sri Lanka have recorded 20,000 and 33,000 bites from poisonous snakes respectively with significant morbidity and mortality.[1] Bangladesh has estimated an annual incidence of 4.3 per 100,000 with a case fatality of 20%.[1] The highest figures in Asia so far come from a community-based survey conducted in Southeast Nepal which revealed an incidence of 1,162/100,000 and a mortality of 162/100,000.[1] The figures quoted above for different South Asian countries are a gross underestimate as a number of cases in South Asian countries unquestionably go unreported.

In the last two decades of the twentieth century the annual death rate from snake bites in Brazil was about 4 per 100,000, in Burma 15 per 100,000 and in the United State about 2,000 per year. In Europe deaths from snake bite are rare.

Snake bite is estimated to account for a tenth as much of the mortality as malaria. This would roughly amount to over 100,000 deaths per annum. Unfortunately, there is no global strategy against snake bite as there is against malaria. There is a tremendous shortage of snake antivenom all over the world, particularly in India and Africa. Research, development and funding for antivenom appear to have sadly lost momentum.

Snake bite is an important occupational hazard in rural areas chiefly affecting farmers, other agricultural workers, herders and fishermen. Open houses and the habit of sleeping on the floor expose individuals to the bites of nocturnal snakes. Bites generally occur on the lower limbs, are common among young men and women and are frequent in the rainy season. Extreme weather conditions such as storms, floods are associated with both an increase in frequency and mortality of snake bites. During the 2007 monsoon flood disaster in Bangladesh, mortality from snake bite was second only to drowning and significantly more than death from diarrhea or respiratory disease.[1] This perfectly illustrates the public health issues and hazards in relation to the important problems in the tropics.

There are over 3,500 species or kinds of snakes in the world, of which about 375 are poisonous.[2-4] The important poisonous families are—

- Elapidae (cobras, kraits, mambas, coral snakes), found all over the world except in Europe.
- Viperidae (true vipers), and the Crotalidae (pit vipers and rattlesnakes).
- Colubridae, seen as a few species with rear fangs in Africa.
- Hydrophiidae (sea snakes) found in the sea close to the coastline, and in large collections of freshwater.

The common varieties of poisonous snakes in India are cobras, the common krait, Russell's viper, the *Echis carinatus* and sea snakes. The cobras include the common Indian cobra and the king cobra. The krait is a small but extremely poisonous snake and includes the common krait and the banded krait. The vipers include the pit vipers, so-called because of a "pit" below the eyes, and the true vipers. Two features common to all poisonous snakes are—

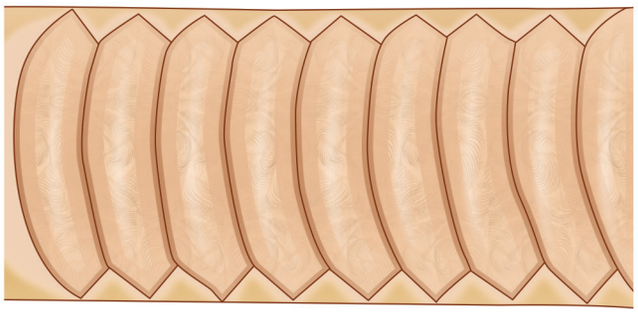

Fig. 1: Ventral scales in a poisonous snake extending right across the belly

Fig. 2: Canalized fang of a Russell's viper to the left grooved fang of a cobra to the right

Source: Vakil RJ, Udwadia FE. Diagnosis and Management of Medical Emergencies. Bombay:OUP; 1982.

1. All poisonous snakes have broad ventral plates on the belly that extend right across (Fig 1). In nonpoisonous snake there are number of small teeth instead of the two fangs of a poisonous snake. If therefore a pin is passed along the margin of the upper jaw and it strikes many small teeth, the snake is harmless; if however two prominent teeth are struck the snake is poisonous.
2. All poisonous snakes have two fangs attached in front to the upper jaw, through which snake venom is injected into the prey. Fangs are specially developed teeth, either grooved or tubular (Fig. 2). Poison glands (secreting venom or poison) are present on either side of the upper jaw. A duct carries the poison from the gland to the base of the fang on either side. When the snake bites, the poison gland is squeezed through the ducts into the fangs, and enters the prey (Fig. 3).

IDENTIFYING FEATURES OF INDIVIDUAL SNAKES

The salient features that help in the identification of the common poisonous snakes of India are given below—

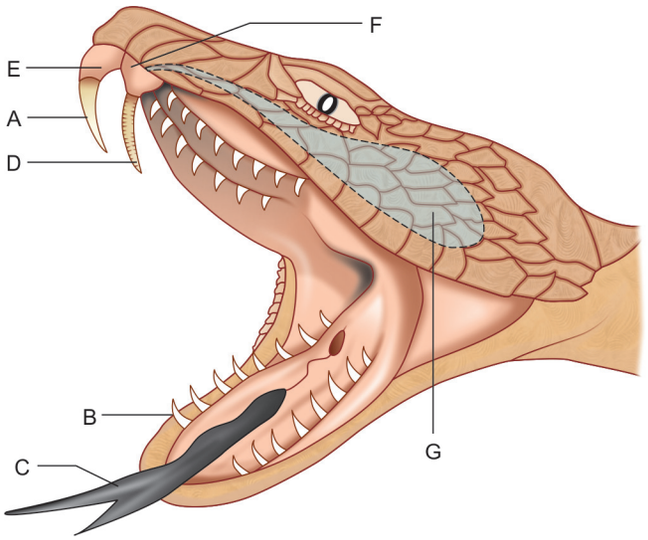

Fig. 3: Head of a Russell's viper showing the poison glands and the cannulated fangs. A—fangs; B—curved teeth; C—tongue; D—orifice of the fang; E—sheath over the fang; F—poison duct at base of the fang; G—poison gland

Source: PJ Deoras—Snakes of India.

Identification of a Cobra (Fig. 4)

It has a well-marked hood, which opens out when the snake is irritated but which may not be evident after the snake is killed. The hood often bears a mark like a ☬ a spot surround by an ellipse.

- The third shield of the upper lips is big and extends from the eye to the shield containing the nostril (this is also observed in coral snakes).
- The shields under the tail are double.
- The Indian cobra quite frequently has two or three series of very dark belly plates under the neck.

Identification of a Viperide (Fig. 5)

- The head is triangular and large and covered by small scales exactly as on the body; the pupils are vertical.
- The pit viper has a sharp pit or depression between eye and nose.
- The pitless viper frequently has marks on the dorsum of the body and head. The head of the Russell's viper has the mark of the letter V with apex in the front, and the body has three rows of large black spots one going down the middle and one down either side. The rows resemble chains (hence also the name Chain Viper).

Identification of a Krait (Fig. 6)

- It is usually 3-feet-long and has broad plates on the belly.
- The head is covered with shields.
- The central row of scales down the back is distinctly enlarged and the prominent scales are more or less hexagonal.
- The plates under the tails are undivided.

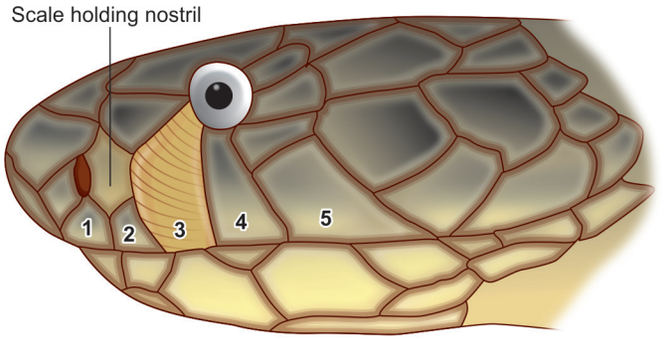

Fig. 4: Cobra head showing the large third labial scale which touches the eye and the scale containing the nostril

Source: Vakil RJ, Udwadia FE. Diagnosis and Management of Medical Emergencies. Bombay:OUP; 1982.

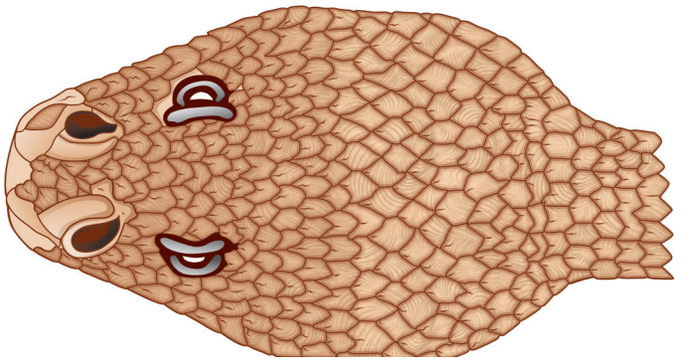

Fig. 5: Scales on the head of a Russell's viper. Note the triangular head with small scales

Source: Vakil RJ, Udwadia FE. Diagnosis and Management of Medical Emergencies. Bombay:OUP; 1982.

COMPOSITION AND EFFECTS OF SNAKE VENOM[5,6]

Snake venoms contain numerous toxic proteins and proteolytic enzymes. The Indian cobra contains a neurotoxin, a hemolysin, a cardiotoxin, cholinesterases, phosphatases, phospholipase B, glycerophosphate, nucleotidase and an enzyme inhibiting cytochrome oxidase. The neurotoxins in cobra venom are polypeptide toxins. α-bungarotoxin and cobrotoxin are postsynaptic ∝ neurotoxins that bind to acetylcholine receptors at the motor end-plate. β-bungarotoxin is a presynaptic β neurotoxin that releases acetylcholine at the nerve endings and then damages the end-plate, so that further release of acetylcholine is arrested.

The viper venom besides containing digestive enzymes, hyaluronidase, also contains a thrombin like factor X and a prothrombin activating factor.

Snake venom produces the following effects—

- *Neurotoxic* This results in a curare-like paralysis of voluntary muscles, a paralysis of the muscles supplied by the cranial nerves, and terminally, paralysis of the brainstem and medulla.
- *Necrotizing* The toxin causes severe inflammation and local necrosis.
- *Hemolytic and hemorrhagic*—The toxin causes intravascular hemolysis and results in severe hemorrhage due to interference and depletion of normal clotting factors.
- *Shock,* which is produced by exudation of fluid into the bitten extremity, by vasodilatation with a generalized increase in capillary permeability, and by severe hemolysis and hemorrhage. In viperine bites, shock may occur before the local features are clinically marked, and before the occurrence of hemorrhage or hemolysis.

The venom of elapids (cobra, kraits, coral snake) chiefly produces a neurotoxic effect, though some degree of hemolysis and local tissue necrosis may also occur.

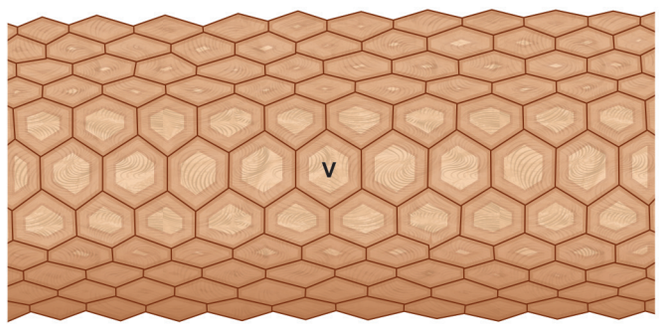

Fig. 6: Back of a Krait showing enlarged vertebrals (V)

The venom of viperidae (vipers) produces a severe local necrotizing lesion, hemolysis, disturbance in the coagulation mechanism with profuse hemorrhage and shock.

CLINICAL FEATURES[7-9]

Before discussing the clinical features the following points deserve notice—

- A bite from a poisonous snake does not necessarily cause envenomation. The patient might have been protected by clothing, or the snake may have emptied its poison on an earlier prey, so that very little or no venom may enter the patient.
- A bite by any snake, even if nonpoisonous, can cause severe fright. A patient may faint from fright. Death has been known to occur from severe fright and acute panic. A history of the patient turning violent and agitated soon after a bite is the result of a hysterical reaction induced by fright; it is not due to envenomation.
- A bite from a poisonous snake leaves two prominent fang marks. Absence of clear fang marks in the wound points to a nonpoisonous snake. The bite in the latter case takes the form of an inverted U (∩) without fang marks.

- Envenomation is invariably far more serious in children than in adults.
- The presence of pathogenic bacteria in the mouth of the snake or on the skin of the victim, can lead to secondary infection of the wound. Tetanus and clostridial infections can complicate bites of poisonous and nonpoisonous snakes.
- If the victim is perfectly well 6–8 hours after a bite, the snake is generally nonpoisonous. Exceptions are observed with some species of viperidae when acute hemolysis or hemorrhagic tendency may manifest 24 hours or even later after a bite. However, even in these patients, some degree of local inflammation around the bite is invariably present.

Cobra Bite

A burning pain is felt over the bite in 5 minutes, often followed by a numbness around the wound which may spread a variable distance up the limb. A red inflamed ring is generally present around the fang marks, but the degree of inflammation is never as marked or necrotizing as with viperine bites.

The systemic effects are observed within 10 minutes to 2 hours of the bite. Early symptoms, before objective neurological features appear, include vomiting, vertigo, circumoral paresthesia, excessive salivation, blurring of vision, and heaviness of the eyelids. This is followed by an increasing weakness and ataxia of the limbs so that the patient is unsteady and finds it difficult to walk. A progressive curare-like paralysis involves muscles supplied by the cranial nerves and skeletal muscles, so that muscle power is reduced and ultimately lost. *Ptosis followed by a varying degree of ophthalmoplegia is generally the first paralytic sign to be observed.* The pupils are increasingly dilated and fixed; bilateral facial palsy occurs. Paralysis of the palate and pharynx makes swallowing difficult, so that secretions collect in the back of the throat. The muscles of the tongue are often involved early; the tongue can be protruded with difficulty, and it feels heavy and stiff so that speech is indistinct. Salivation is often increased, and when associated with an inability to close the mouth and the lips, leads to continuous dribbling of saliva. Weakness of the muscles of the neck allows the head to fall forward on the chest if the patient is made to sit up (broken-neck sign). The skeletal muscles are soon involved leading to a well-nigh total paralysis. Ultimately, paralysis involves the muscles of respiration (the intercostals and diaphragm) so that breathing is shallow and irregular. The patient hypoventilates and has both hypoxia and hypercapnia. Involvement of other vital centers in the brainstem particularly the vasomotor center leads to hypotension and shock.

The patient is generally conscious to the end, perfectly aware and helpless against the relentless increase in the paralysis that ultimately kills him. Death generally occurs within 4–12 hours of the bite; it may however occur within an hour, or may be delayed for 72 hours. Some degree of hemolysis and a mild bleeding tendency may be observed in those who live more than 24 hours. If the patient does not die, paralysis quickly recedes and complete recovery without any sequelae occurs.

Krait Bite

The symptoms are similar to cobra bite, with the addition of severe abdominal pain and cramps.

Sea Snake Bite

Headache, sweating, vomiting, thirst, heaviness of the tongue are first observed. Within 30 minutes to 4 hours, there is a painful stiffness of the muscles; trismus is frequent. This phase is followed by a generalized flaccid paralysis. Myoglobinuria following rhabdomyolysis occurs within 3–8 hours after the bite and may lead to renal failure. Hyperkalemia often results due to the release of potassium from damaged muscles; it can lead to cardiac arrest.

Viperine Bites

Local Effects

These are marked and are observed very often within a few minutes of the bite. Severe pain, increasing redness, edema and bulla formation are observed spreading outward from the fang marks. A serosanguinous discharge oozes from the wound. The necrotizing inflammation involves the soft tissues, may even involve muscle, and may be severe enough to cause gangrene. It creeps up the limb if the bite is on an extremity. Skin lesions may be observed.

Systemic Effects

- *Acute circulatory failure* Shock with pallor, tachycardia, sweating, hypotension, restlessness and oliguria can occur within a few hours. Several factors contribute to shock. These include hemolysis, extravasation of fluid into the bitten limb, a generalized increase in capillary permeability and hemorrhage. In many patients shock occurs before all the above features are clinically apparent. It is probably due to specific factors within the venom that directly induce acute circulatory failure.
- *Severe intravascular hemolysis* Hemolysis causes a profound fall in hemoglobin, icterus, hemoglobinemia, hemoglobinuria and acute tubular necrosis, resulting in renal failure.
- *Disturbances in clotting mechanism with hemorrhage* Bleeding typically takes the form of bleeding from the gums and tooth sockets (often the first sign), epistaxis, hematuria, hematemesis, and rectal bleeding. Bleeding can also occur into various organs, such as the brain, lung, into the pleural space or into muscle and tissue. Disseminated intravascular coagulopathy can occur. Bleeding in some instances may only take place from one site, e.g. a severe rectal bleed, or bleeding from the urinary tract. Though bleeding generally occurs within a few hours, it occasionally may occur 24 hours or even later

after a bite. Bleeding from one or more sites may be the sole manifestation of a viperine bite.

- *Fever* of 100–104°F, with well-marked leukocytosis (20,000–40,000/mm^3), is invariably present. Vomiting is early and frequent; rarely seizures may also occur.
- *Acute renal failure* is an important and frequent complication of viperine bites. It can result from acute circulatory failure and shock, from acute intravascular hemolysis, from disseminated intravascular coagulopathy or from a combination of factors. It is most often due to acute tubular necrosis.

Death when it occurs in viperine bites, generally occurs in 12–24 hours.

MANAGEMENT[8-11]

Unfortunately, envenomation from snake bite chiefly occurs in rural India and not in the large towns where critical care units or emergency departments are available. What is more, many patients after being bitten by a poisonous snake prefer to go to traditional healers rather than be treated by allopaths or be treated in hospitals.

Critical care or at least basic well-directed medical attention can however make a difference between life and death in patients suffering from severe envenomation following a snake bite. Critical or emergency care whenever possible is mandatory under the following circumstances—

- Systemic effects of envenomation are present following a snake bite. The patient should be admitted to the intensive care unit (ICU) even if systemic features are mild. Sudden clinical deterioration can occur, particularly in a krait or cobra bite.
- Local inflammation around the bite is marked soon after a snake bite, even in the absence of systemic features. Bites causing acute inflammation within a matter of minutes or hours are invariably due to poisonous snakes. Two telltale fang marks are generally visible. They are generally viperine bites, and sudden severe bleeds may occur within the first 24 hours.

First Aid

It is generally agreed by all experts in the field that snake bite victims should be transported as quickly as possible to a healthcare center or hospital, where they can be clinically evaluated and antivenom promptly administered if the bite is found to be poisonous. In fact the time of transfer has been shown to be a crucial determinant of mortality and morbidity following a bite from a poisonous snake. Delayed antivenom administration is unquestionably associated with increased mortality and increased complications. The victim should be reassured, the bitten limb immobilized with a makeshift splint (of the lower limb) and sling (for the upper limb). The patient should not be allowed to walk as muscular contractions of the lower limbs can promote spread of the poison.

Traditional measures as incising the area of the bite, attempts to suck poison, application of herbal medicine are not only useless but also dangerous as they can lead to secondary infection of the wound.

The application of a tourniquet proximal to the bite though useful as an emergency measure is not likely to help if admission to a health center or hospital is delayed beyond 30 minutes. The continuous application of a tourniquet is contraindicated as it can lead to gangrene, increased fibrinolysis, bleeding distal to the tourniquet, compartment ischemia and increase in the local symptoms of envenomation. *The current recommendation is to avoid the use of a tourniquet.* Instead the bitten limb is immobilized by bandaging it tightly with a crepe bandage starting from the toes or fingers and extending the bandage up to the knee or elbow. A splint is incorporated into this dressing for better immobilization. This method was developed by Struan Sutherland and his colleagues in Australia. It should be used only for cobra and krait bites, whose poison is chiefly neurotoxic. It should not be used for viperine bites as tight bandaging could worsen edema and tissue necrosis of the limb.

In conclusion, first aid basically consists of immobilizing the bitten limb as described above, preventing the patient from walking or using the bitten limb and arranging for quick transport of the patient to a health center or hospital, where the patient is quickly evaluated and antivenom promptly administered if the bite is felt to be poisonous.

During urgent transport to a hospital, emergency department or local dispensary, care is taken to avoid aspiration if the patient is vomiting. Oxygen is administered if there is cyanosis and adrenaline 0.5 mL subcutaneously administered for autonomic disturbances or hypotension. Cardiopulmonary resuscitation may be necessary during transport, in desperate situations.

The immediate priorities in severe envenomation after admission to the emergency department of a hospital or to a critical care unit are—

- Cardiorespiratory support, and also support to other organ systems.
- *Neutralization of the poison with antivenin* Both these priorities should be addressed more or less simultaneously.

A large peripheral venous line is promptly secured and blood sent for a blood count, hematocrit, platelet count, bleeding time, clotting time, prothrombin time, aPTT, electrolytes, urea and creatinine. In viperine bites presenting with bleeding, a coagulation profile is necessary. The reticulocyte count and tests for hemoglobinemia and hemoglobinuria should be done in patients with hemolysis. A urine examination is done and an intake output carefully charted. A central venous line is secured for administration of fluid, drugs and for monitoring the central venous pressure. Arterial blood pH, and blood gases are estimated, and the patient's ECG monitored.

Neutralization of the Poison

The only effective treatment against venom that has entered the circulation is its neutralization by the use of antivenin.

Ideally, to be most effective, antivenin should be given as soon as possible. It is however never too late to administer antivenin provided systemic signs of envenomation are present. It has thus been reported to be effective when given to patients who remain defibrinated weeks after a viperidae bite. In India, the Haffkine Institute in Mumbai prepares a polyvalent antisnake venom serum. This is prepared by hyperimmunizing horses against the venoms of four common poisonous snakes: cobra, Russell's viper, common krait, and the Echus (saw-scaled viper). Each mL of the concentrated serum neutralizes the following quantities of dried venom when injected along with the venom in white mice; cobra 0.6 mg, Russell's viper 0.6 mg, common krait 0.45 mg, Echus 0.45 mg. The serum is lyophilized, and to be reconstituted has to be dissolved in distilled water.

Use of Antivenin[10-14]

A sensitivity test is first performed. If the patient is not sensitive, 5 mL of the reconstituted polyvalent serum is injected locally around the wound. Local infiltration of antivenin should never be done into a finger or toe, as it can induce sloughing and gangrene.

The next step is the systemic use of antivenin. This is preferably preceded by the subcutaneous injection of 0.5 mL of 1 in 1,000 adrenaline, as also by an injection of an antihistamine. Antivenin should as far as possible be administered intravenously, particularly in patients who are seriously ill or in shock. Hundred mL of the polyvalent serum is added to 300–500 mL N saline, and given as an infusion over 1–2 hours. This dose may be repeated twice or even more frequently in serious life threatening situations.

In patients who are sensitive to the polyvalent serum, a rapid desensitization should be attempted. 0.05 mL subcutaneously is first given; this is followed by progressively increasing doses till 2 mL is given intramuscularly. A further gradual increase in intramuscular dosage to 10 mL and then to 40 mL is made. This may need to be done under cover of adrenaline, antihistamine and corticosteriods. If no reaction occurs to a large intramuscular dose then 75–100 mL of the polyvalent serum is diluted in 500 mL N saline, and given as a slow infusion over 2 hours. A careful watch should be kept for untoward reactions.

In small children in whom it may be impossible to quickly find a vein, polyvalent serum should be given intramuscularly. The dose in children is the same as in adults, since envenomation in children is always more serious than in adults. About 60–100 mL (divided doses) is given intramuscularly with hyalase, to help absorption. If however a vein can be secured, the same dose is given as an infusion in normal saline over 2 hours. Intravenous administration whenever possible is to be preferred to the intramuscular use of the antivenin.

The use of antivenin is followed by a prompt reversal in the systemic features of envenomation. Spontaneous bleeding in viperidae bites stops within an hour and the coagulation profile reverts to normal within 6–12 hours. Systemic envenomation can however recur after hours or even days of initial good response. This is due to the continued absorption of the venom from the wound after it has been initially cleared from the blood stream by the antivenin. The dose of antivenin should then be repeated, and the patient observed closely for 3–5 days.

The success of antivenom depends on the ability of the immunoglobulin to bind and remove poisonous toxins from the body. The efficacy of immunoglobulin in restoring cardiovascular stability and hemostasis is well-established; however, the ability of antivenom to prevent local tissue necrosis in viperine bites and severe neurotoxicity is controversial. Thus it has been observed that the administration of antivenom to krait bite victims, who already have respiratory paralysis, does not reverse paralysis. Perhaps treatment outcomes vary with the geographical areas, as the composition of venom and the antigenic properties of toxins can be variable across the range of a given snake species. Indian antivenoms are produced using venoms from snakes captured in the small geographical areas within the state of Tamil Nadu. It is possible that these antivenoms may not be as effective in other regions of the country. Most of the antivenoms that have been used routinely in South Asia have not been subjected to preclinical testing, nor to evaluation in clinical trials.

Cardiorespiratory Support

This is of vital importance in seriously ill patients. Immediate endotracheal intubation with ventilator support is necessary in cobra or krait bites that cause a curare-like paralysis. It is important to secure and protect the airway and anticipate respiratory failure in these patients. In bites of Elapidae causing a curare-like paralysis, prostigmine 2.5–5 mg intramuscularly has been tried (as in myasthenia gravis). Prostigmine generally produces little or no improvement. It should never be relied upon to prevent respiratory paralysis in these patients. Ventilatory support is also necessary in patients in severe shock, so often observed with viperine bites. Intensive respiratory care goes pari passu with ventilatory support.

A sufficient volume load should be given to ensure a left ventricular filling pressure of 15 mm Hg. This may require the use of a Swan-Ganz catheter. Inotropic support is also often necessary in these patients.

Support to Other Systems

- Acute hemolysis is treated by small packed cell transfusions of carefully matched blood.
- Severe hemorrhage due to deficiency of clotting factors is treated by infusions of fresh frozen plasma: 8–10 units or more may be necessary. When fibrinolysis occurs following snake bite, the use of epsilon aminocaproic acid 0.1 g/kg in a slow intravenous infusion is of help. Cryoprecipitate should be infused (8–10 units or even more), if fibrinogen levels are low.
- Renal function must be supported by care over fluid and electrolyte balance, and avoiding the use of nephrotoxic drugs. Acute tubular necrosis with a mounting serum

creatinine requires hemodialysis till such time as kidney function returns to normal.

- Metabolic acidosis if present is countered by attempts to increase oxygen transport, and improve tissue perfusion. Intravenous sodium bicarbonate may be given so that the arterial pH is not less than 7.3.

Care of the Wound and Surrounding Inflamed Area[15]

Strict asepsis after admission to the unit is necessary. The wound should be washed with Condy's lotion or potassium permanganate, and suitably dressed with an antibiotic ointment. Tetanus toxoid should always be administered to prevent tetanus. Crystalline penicillin in a dose of 1 milion units is given intravenously 6 hourly. If Gram-negative organisms are present on examination of the discharge from a wound, a third generation cephalosporin, like ceftazidime 1 g intravenously 8 hourly, may be given.

Pain in and around the wound is relieved by analgesics. Morphine is contraindicated in cobra and krait bites.

Cryotherapy has been advocated locally in the treatment of viperine bites. It consists in packing the bitten extremity with freshwater ice in plastic bags, whilst keeping the rest of the body warm. The objective is to chill the tissues (and not freeze them) in order to retard the local proteolytic and enzymatic activity of the venom. It is important not to pack the bitten extremity in freshwater ice during administration, the antivenin, and for 12 hours after administration, as reaction of the antivenin with the venom may otherwise be interfered with. Current experience however throws doubt on the efficacy of cryotherapy. It could do more harm by increasing tissue necrosis.

Use of Corticosteroids

Good results have been reported with the use of corticosteroids. In viperine bites both local and systemic effects of envenomation seem to be reduced. A correct and unbiased appraisal of the efficacy of corticosteroids in snake bites is however difficult. In severely ill patients, particularly those in shock it is advisable to give hydrocortisone hemisuccinate 300 mg intravenously, followed by 300 mg in a slow infusion over 24 hours. 100 mg intravenously 8 hourly may then be given for the next 2–3 days.

TREATMENT OF LATE COMPLICATIONS

Late complications like renal shutdown, local gangrene, or severe tissue necrosis need expert specialized management. Hemodialysis is often necessary for the management of acute renal failure following viperine bites. *In the southern part of our country, snake bites would constitute one of the most important causes of acute renal failure necessitating the use of hemodialysis.* The management protocol used for snake bites has been summarized in Box 1.

Box 1: Summary of management protocol in snake bites

- Neutralization of poison promptly with antivenin
- Cardiorespiratory support—
  - Immediate endotracheal intubation with ventilator support in cobra/krait bites causing curare-like paralysis, and in patients in severe shock following viperine bites
  - Maintain left ventricular filling pressure around 15 mm Hg with use of sufficient volume load
  - Inotropic and/or vasopressor support may be required
- Support to other organ systems—
  - Treat hemolysis with transfusions of packed cells/whole blood
  - Deficiency of clotting factors treated by infusions of fresh frozen plasma and cryoprecipitate. Epsilon aminocaproic acid may be useful for fibrinolysis
  - Support renal function by maintaining fluid and electrolyte balance, and avoiding use of nephrotoxic drugs
  - Counter metabolic acidosis
- Care of the wound and surrounding inflamed area
- Use of tetanus toxoid, antibiotics, analgesics
- Use of corticosteroids
- Treatment of late complications, e.g. renal shutdown, local gangrene or severe tissue necrosis

OTHER POISONOUS BITES

Scorpion Sting[16-18]

Some species are deadly poisonous. The poisonous species encountered in Western Maharashtra is the—Indian red scorpion Mesobuthus tamulus. In North Africa the yellow scorpion (*genus liturus*) is chiefly responsible for lethal envenomation.

The venom from a scorpion sting deposit in the subcutaneous tissue may take as long as 6–8 hours for complete absorption. Elimination of the venom by the body is slower, with estimated half-life of 4.2–24 hours.

The local effects of envenomation following a scorpion bite are burning pain, inflammation and ecchymosis. Scorpion venom stimulates the release of catecholamines and acetylcholine. Early symptoms include vomiting, sweating, abdominal colic, diarrhea, salivation, piloerection and occasionally priapism. A tachy-brady rhythm may occur. Ultimately a shock like state with hypotension and tachycardia evolves. In a large study conducted over several years in a hospital in Mahad (situated on the outskirts of Mumbai), hypertension was observed in 27% of patients and pulmonary edema, at times fulminant, in 18%.[16,17] The cause of hypertension in some patients is related to stimulation of the α-adrenergic receptors by the venom. The venom also has a toxic effect on both the left and right heart. Severe left ventricular dysfunction leads to a raised pulmonary capillary wedge pressure with

resulting pulmonary edema.[18] The cardiotoxic effect of the venom can also cause marked bradycardia and arrhythmias. The venom over a period of time can result in multiple organ dysfunction. Death generally results from acute circulatory failure or from fulminant pulmonary edema.

Treatment

Mortality depends on the time lag between the scorpion sting and the start of medical treatment. It also depends to an extent on the quality of care offered. Death occurs in 5–35% of patients.

If the patient is brought to the unit within 30 minutes of the bite, cryotherapy in the form of application of ice in plastic bags around the bitten area, may help to retard the local proteolytic effects of the poison.

Scorpion antivenin if available should be promptly administered intravenously. Experimental and clinical studies suggest that it could reverse the circulatory, metabolic and ECG changes caused by the venom. Unfortunately scorpion antivenin is even more scarce than snake antivenin.

Supportive treatment is imperative, particularly with regard to the cardiorespiratory system. Hypovolemic shock is treated by a volume load. Severe pulmonary edema particularly when associated with hypertension responds to an intravenous infusion of nitroprusside. Severe left ventricular dysfunction needs dopamine and dobutamine support.

The study in Mahad referred to earlier suggests that prazosin (an alpha blocker) in a dose of 250 µg in children and 500 µg in adults given 3 hourly is of considerable use. It controls both hypertension and pulmonary edema. Patients receiving prazosin early in this study did not develop pulmonary edema.[16,17]

Centipede Bite

The clinical features are similar to a scorpion bite and may prove fatal, particularly in children. Local inflammation around the bite is followed by restlessness, salivation, diaphoresis with a shock-like state that may culminate in death.

Treatment is symptomatic; cardiorespiratory support with management of the shock-like state is important.

Bee and Wasp Stings

Multiple stings are observed particularly in hikers who unwittingly disturb a beehive. The usual reaction to a sting is a sharp pain followed by a local wheal and severe edema, particularly if the sting is on the face. A sting into a peripheral nerve leads to a temporary loss of function of the nerve. With multiple stings or in hypersensitive individuals, a picture of anaphylactic shock is observed—severe urticaria, bronchial spasm, and hypotension, followed at times by cardiac arrest.

If brought as an emergency to the ICU, adrenaline in a dose of 0.75–1 mL is injected subcutaneously. If hypotension and a state of anaphylaxis prevail, adrenaline may need to be given intravenously (see Chapter Anaphylactic Shock), and emergency resuscitation with cardiorespiratory support should be promptly initiated. The airway should be quickly secured by endotracheal intubation in patients with increasing urticaria involving the skin and mucosa. Intravenous hydrocortisone and antihistamines are of help particularly in patients with severe urticaria.

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CHAPTER 68

Drowning

INTODUCTION

Drowning is asphyxiation resulting from submersion in a liquid (invariably water).

In India, drowning accidents are most often related to sheer rashness when swimmers or holiday makers who can barely swim venture into an area of the sea in spite of an express warning pointing to the hazards of doing so. The paucity of trained life guards along the coastline compounds the problem.

The use of alcohol can be an important risk factor, as alcohol reduces the ability to deal with emergency situations, impairs coordination as also the cognitive ability to quickly realize the gravity of a dangerous situation.

Lack of appropriate supervision by adults is an important cause of drowning accidents in children or in those learning to swim in swimming pools.

Perhaps the most ghastly of drowning tragedies occur in boating accidents. The commonest cause of boating accidents in India is overcrowding of ferries and boats during crossing of rivers. Collision on the high seas between ships or between ships and a rugged coastline or against rocks or an iceberg (as with the Titanic) can lead to deaths of several people from drowning.

Finally, medical catastrophes can contribute to drowning accidents. These include seizures while swimming, cerebrovascular accidents or a cardiac arrest following myocardial infarction.

The official nomenclature for submersion injuries was laid down during the World Congress on Drowning[1] in 2002. The term fatal drowning is used to describe death by submersion in water and near-fatal drowning to describe at least temporary survival after respiratory impairment from submersion in water. However, the terms drowning and near-drowning often continue to be used as synonyms for fatal and near-fatal drowning respectively.

PATHOPHYSIOLOGY

Two major mechanisms are responsible for morbidity and mortality in drowning—severe hypoxia and hypothermia. The effects of both are additive. At times hypoxia is the sole cause of death as in warm tropical waters and at times hypothermia plays an equally important role. For example, deaths after the sinking of the Titanic were more because of hypothermia due to exposure to extremely cold water rather than to the inability to float.

The role of hypoxia and hypothermia are considered separately in the ensuring discussion.

Role of Hypoxia

The following sequence is believed to occur in most cases.[2] After immersion, there is a period of voluntary breath holding as the victim's mouth and nose are below water. This is followed by a phase of intense laryngeal spasm which prevents breathing; the laryngeal spasm is triggered by the presence of water in the pharynx and/or larynx. In about 10% of patients, the unrelenting laryngeal spasm leads to asphyxia and death from hypoxia with very little water entering the lungs. In most victims, however, the laryngeal spasm abates followed by involuntary breaths, resulting in aspiration of quantities of water into the lung. Water may also be swallowed which again is regurgitated and aspirated into the lungs. The severe hypoxia renders the patients unconscious; death results from hypoxic cardiac arrest.

Freshwater as in lakes, ponds, swimming pools and saline water as in the sea, act differently on the lungs. Freshwater acts

by inactivating surfactant and by damaging type II pneumocytes, thereby preventing the formation of surfactant.[3] This results in damage to the alveolar capillary membrane and leads to acute respiratory distress syndrome.[3] Atelectasis due to increased surface tension and bronchoconstriction also occur. On the other hand, aspiration of hypertonic seawater into the alveoli draws fluid from the plasma into the alveoli resulting in pulmonary edema in the presence of a reduced intravascular volume. Surfactant damage and damage to type II pneumocytes by hypertonic saline may contribute to pulmonary edema.

Notwithstanding the different pathogenetic mechanisms that injure the lung following freshwater and saltwater aspiration, failure in gas exchange, hypoxia, hypercapnia and death from cardiac arrest constitute the end-result.

In near-fatal drowning, bacterial pneumonia, chemical pneumonitis, barotraumas and oxygen toxicity during resuscitation can cause complications and respiratory deterioration in the post-resuscitation period.[4] In near-fatal accidents effects on other organ systems are chiefly the result of prolonged hypoxia.

Effects on the central nervous system strongly influence prognosis. Hypoxic encephalopathy is the single most important complication and is identical to hypoxic brain damage from other causes. It includes cerebral edema, focal areas of necrosis and ischemic changes most marked in the cerebral cortex, hippocampus and cerebellum. Hypoxic encephalopathy may ultimately cause death or lead to persistent coma, seizures, aphasia, cortical blindness and varying disturbances in cognition. Predicting outcome following hypoxic encephalopathy may be impossibly difficult, though several studies have attempted to do so.[5,6]

In near-fatal drowning, cardiac complications often occur. These include atrial fibrillation, and prolonged QRS and QT intervals. Various arrhythmias including ventricular fibrillation and asystole can occur, ultimately causing death. Focal myocardial necrosis observed at autopsy is believed to be related to excessive catecholamine release, similar to that observed in patient with pheochromocytoma.

Renal effects in near-fatal drowning include acute tubular necrosis and hemoglobinuria. Metabolic acidosis is often present due to increased lactic acid in the blood.

Serum Electrolyte Changes

It used to be emphasized some decades ago that submersion in freshwater led to hemodilution, hemolysis, hyperkalemia and hyponatremia, and that these changes could contribute to ventricular fibrillation and death. Submersion in hypertonic saltwater (seawater) was believed to draw water from the blood and interstitial compartment into the alveoli causing hypernatremia and pulmonary edema. Currently, it is believed that in near-fatal drowning the body corrects these alterations so that the clinical impact of the electrolyte changes is minimal.[7]

Hematological Effects

Near normal hemoglobin values have been generally observed in near-fatal drowning. However, disseminated intravascular coagulopathy has been described as a complicating factor in freshwater drowning.[8]

Infectious Complications

Near-fatal drowning victims may have their clinical course complicated by infectious complications, the most frequent and important being pneumonia. Pneumonia is due to aspiration of contaminated water, gastric contents and mouth contents. Gram-positive, Gram-negative organisms as also fungi have been shown to be causative agents. Most pneumonias occur following warm water submersion as most organisms generally do not survive in very cold waters.

Hypothermia

As mentioned earlier, hypothermia plays an important role in drowning accidents in cold climes, particularly in winter months. The effects of hypothermia are complex. On the one hand, survival can occur after long submersion if the victim has been submerged in icy water, and the core body temperature reduced quickly and the brain metabolic activity slowed down rapidly so as to prevent hypoxic brain damage. On the other hand, humans tolerate hypothermia poorly as is seen in deaths after the sinking of the Titanic. Submersion in very cold water can cause death in three ways—first, by inducing a vagally mediated asystole (immersion syndrome); second, by producing arrhythmias, particularly ventricular fibrillation. These arrhythmias are refractory to resuscitative attempts unless the core temperature of the body is sufficiently raised. Thirdly, a fall in core temperature can cause a loss of consciousness, which leads to aspiration of water in the lungs.

CLINICAL FEATURES

In the history, it is important to determine the duration of submersion, whether submersion was in freshwater or seawater, roughly the temperature of the water, whether submersion occurred during swimming, following diving or because of a boat accident. A knowledge of comorbid conditions affecting the victim is of help.

Physical Examination

Physical examination must be brief, chiefly concentrating on vital signs, and on possible injury, in particular to the cervical spine. Detailed examination may be performed well after resuscitative efforts have been established.

Tachypnea and tachycardia are the chief physical signs in near-fatal drowning accidents. The patient may however at times be apneic or have gasping irregular breathing. There may be auscultatory signs of pulmonary edema with frothing at the mouth. The temperature is often subnormal and physical findings associated with hypothermia or cerebral hypoxia may be evident.

Modell and Conn have classified near-fatal drowning victims into three categories.[9]

Category A Patients are alert one hour after presentation in the emergency department. These patients do well neurologically.

However, these patients should be kept under observation as pulmonary edema (which may be quite severe), can develop a few hours later.

Category B Patients are obtunded but arousable. Most of these patients survive and severe neurological sequelae generally do not occur.

Category C Patients are comatose with abnormal respiration and abnormal response to pain. Category C is further divided into C1 decorticate posturing; C2 decerebrate posturing; C3 flaccid state.

Patients in the C category have a very high mortality and survivors show severe neurological sequelae.[10]

Laboratory Examination

Laboratory studies include routine blood and urine tests, blood chemistry, arterial blood gases, serum lactate, serum creatinine, prothrombin time, partial thromboplastin time and electrocardiography.

An X-ray of chest and X-ray of the cervical spine (if there is a suspicion of injury) should be done. Radiological examination of the chest shows evidence of pulmonary edema in most patients.

TREATMENT

Initial Cardiopulmonary Resuscitation

Cardiopulmonary resuscitation in apneic and pulseless victims takes precedence over all other procedures and should be promptly initiated as soon as the patient is brought out of the water. It should be continued uninterrupted during transport to a hospital's emergency department or intensive care unit (ICU) (see Chapter Cardiopulmonary Resuscitation and Cerebral Preservation in Adults). Once in hospital, either in the emergency department or the ICU, advanced cardiopulmonary support is initiated.

How long should resuscitation continue? Resuscitation should be continued in victims of cold water submersion at least until the victim has been rewarmed. Core temperature (measured through a low reading rectal thermometer) should be measured promptly and monitored throughout the period of resuscitation. All drowning victims with cardiopulmonary arrest and hypothermia should be rewarmed rapidly to a temperature between 32°C and 34°C and then maintained at that level.

The following procedures are used for rewarming, depending on facilities and expertise available in the hospital to which a patient is admitted—

- Removal of wet clothing at the site of accident or in the ambulance with inhalation of warm oxygen.
- In the hospital, warmer blankets are used and heated oxygen inhaled. Infusing warm fluids intravenously and performing gastrointestinal irrigation with warm fluids also helps. If available, hemodialysis and peritoneal lavage can help quicker rewarming.
- In patients who have severe hypotension, especially in patients with circulatory collapse, cardiopulmonary bypass can rapidly achieve rewarming with rapid elevation of the core temperature. This method also corrects metabolic acidosis which is often present. Cardiopulmonary bypass obviously should be used only when both expertise and experience are available.

How long does one resuscitate victims of normal or warm water submersion? This is difficult to answer. The decision to terminate cardiopulmonary resuscitation may depend on factors peculiar to a given patient. Inability to resuscitate a patient over 30 minutes generally is an indication to stop resuscitative attempts.

Once a patient has reached hospital and is either in the emergency department or in the ICU, advanced cardiopulmonary support should be forthcoming. An apneic patient or patient with severe pulmonary edema is promptly intubated and put on ventilator support. It is important to use lung protective measures during mechanical ventilation—low tidal volumes of 5–7 mL/kg, not allowing plateau pressures to be greater than 30 cm H_2O.

In patients with milder pulmonary edema who are not very hypoxic noninvasive ventilatory support can be given a try (see Chapter Acute Respiratory Failure in Adults and Chapter Mechanical Ventilation in the Critically Ill).

Other important therapeutic measures include the following—

- Correction of fluid and electrolyte disturbances.
- Correction of metabolic acidosis. The lack of appreciation of this factor has led to unfortunate fatalities. 7.5% sodium bicarbonate is administered intravenously if the arterial pH is less than 7.25. Some drowning victims have a respiratory acidosis; this is corrected by ventilatory support.
- Use of drugs—
  - Frusemide is of use in patients with pulmonary edema.
  - Victims who in addition to pulmonary edema have severe bronchoconstriction are helped by nebulizing duolin and by the use of intravenous hydrocortisone.
  - Febrile victims are empirically given a broad spectrum antibiotic and treated symptomatically to reduce any rise in temperature.
  - Symptomatic treatment with vasopressors and/or inotropes is necessary to maintain blood pressure during early emergency treatment.
  - Cardiac arrhythmias if present need appropriate management.

The World Congress on Drowning in 2002[1] recommended the following interventions following cardiopulmonary arrest from drowning—

- Restoration of spontaneous circulation is of the highest priority.
- Core temperature should be monitored.
- In patients with cardiopulmonary arrest a core temperature of 32–34°C should be maintained for a period of 12–24 hours. The use of therapeutic hypothermia

has been substantiated in outpatient cardiac arrest in two randomized controlled studies published in 2002. Hyperthermia should be prevented at all costs during the acute recovery period.

- Seizures should be diagnosed and appropriately treated.
- Hypoxemia and hypotension should both be avoided.

Finally, it is important to remember that the sudden occurrence, while swimming, of an acute myocardial infarction, a cardiac arrhythmia, an epileptic seizure or a stroke can precipitate a drowning accident. It is equally important to realize that in older subjects, a myocardial infarct or a dangerous arrhythmia can occur subsequent to severe hypoxia and exhaustion following a drowning accident.

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CHAPTER 69

Heat Stroke

INTRODUCTION

Heat stroke is an acute calamity produced by high environmental temperature. A relatively high humidity is a predisposing factor as is also a prolonged exposure under a hot sun. The condition is characterized by a failure of the thermoregulatory mechanism of the body whereby the heat gained by the body is far more than that lost, so that the body temperature rises, the core temperature exceeding 40°C.

Heat stroke is more common in the very hot summer months of hot tropical equatorial countries or the hot desert lands in the Middle East, where environmental temperature may be well past 45°C. Heat waves in Europe have also led to heat stroke, particularly in elderly individuals living alone in poorly ventilated apartments.

The thermoregulatory center at very high ambient temperatures is overwhelmed even if it is functioning normally, so that the heat gained through the hot environment is far in excess of the heat lost.

Heat strokes can also occur following endogenous heat production during strenuous exercise or exertion. Heat production during exercise or exertion ranges from 300 kcal/hour to 900 kcal/hour. Even in conditions allowing maximum evaporation of sweat not more than 500–600 kcal/hour of heat may be lost. The progressive heat gain in these circumstances leads to a progressive rise in the core temperature of the body culminating in a heat stroke.

Endogenous heat production can also be increased by fever, thyrotoxicosis, or the hyperactivity associated with amphetamine and hallucinogen use. Under the above circumstances even healthy individuals with normal thermoregulatory centers may develop heat stroke during exercise in warm ambient surroundings. Exertional heat stroke is typically seen in younger individuals, athletes, marathon runners exercising at higher than normal ambient temperatures. On the other hand, classical heat stroke due to very high ambient temperatures is more often observed in older individuals.

Precipitating factors are a poorly functioning thermoregulatory center with impaired ability to provide adequate heat loss, poor sweating, dehydration and impaired cardiovascular function. A poor cardiovascular performance leads to a decreased blood flow to skin and muscles, thereby decreasing the movement of heat from the core to the environment.

Many drugs are known to predispose to heat stroke. These include phenothiazines, butyrophenones and antiparkinson medications. Hypothalamic lesions also impair thermoregulation.

PATHOPHYSIOLOGY

Excessive rise in the body temperature leads to cellular toxicity and ultimately to cell death. The critical thermal maximum is a temperature above 42°C.[1] Cellular damage and cell death are ultimately due to cessation of mitochondrial and enzymatic activity and to instability of the cell membrane. The effect on cell structure and metabolism is widespread and occurs in all organ systems of the body.[2]

The stress produced by heat to the body provokes a systemic inflammatory response characterized by activation and increased circulation of tumor necrosis factor α, IL-2, IL-6, IL-8, IL-10, IL-12 and interferon gamma.[3]

Bacterial translocation from an ischemic gut leads to Gram-negative endotoxemia and further aggravates the inflammatory response. Endothelial injury is an important

feature of heat stroke. It activates the coagulation cascade which is responsible for microthrombi in the small vessels of all organ systems thereby perpetuating multiple organ dysfunction and failure. Dehydration when there has been excessive sweating and also metabolic acidosis worsen the situation. Metabolic acidosis is mild in classic heat stroke except terminally, whereas metabolic acidosis may be the presenting feature in heat stroke induced by exercise or exertion in high environmental temperature.

Effects on the Central Nervous System

Though all organ systems are affected by excessive heat stress, the clinical manifestations of striking importance are related to the central nervous system (CNS). Thermal toxicity leads to cell death within the brain and spinal chord, cerebral edema and focal hemorrhage. These changes result in stupor progressing to coma and seizures. The Purkinje fibers of the cerebellum are particularly vulnerable to the effect of heat. Progressive cerebellar atrophy has been documented in high resolution computed tomography (HRCT) of the head and by magnetic resonance imaging (MRI).

Cardiovascular Effects

Cardiac output is increased due to lowered peripheral vascular resistance and increased vasodilation. Dehydration occurs frequently from excessive sweating, sweat rates being at times as high as 1.5–2 L/hour.[4] Not all patients sweat profusely; in fact, some sweat poorly and in these patients the core temperature of the body rises both faster and higher. Hypotension occurs frequently. As the condition progresses and worsens there is myocardial depression, a fall in cardiac output and the frequent occurrence of tachyarrhythmias. Focal hemorrhage and necrosis within the epicardium and within myocardial muscle fibers is present at autopsy.

Renal Effects

Renal damage occurs in all patients with heat stroke; it is potentiated by rhabdomyolysis, hypotension and dehydration. Acute tubular necrosis is a well-known complication.[5] Very high creatinine phosphokinase values increase the risk of renal failure.

Effect on the Musculature

Muscle necrosis occurs as a direct result of high temperature. Muscle damage is more marked in heat stroke related to exercise or exertion. Rhabdomyolysis is extremely common with exertional heat stroke but may also occur in classic heat stroke.

Hematological Effects

There is a leukocytosis which often leads to the wrong suspicion of infection. A bleeding diathesis is invariably present, particularly in fatal cases. It is due to thrombocytopenia, direct inactivation of platelets due to heat, poor platelet aggregation and most important of all by the development of disseminated intravascular coagulation (DIC) which occurs most frequently on the 2nd or 3rd day of the heat stroke. DIC is due to activation of the coagulation cascade caused by the stress of heat. When fully evolved it worsens multiple organ dysfunction and is invariably fatal.

Pulmonary Effect

Acute respiratory distress syndrome (ARDS) is a well-known complication of heat stroke. Pulmonary edema may also result from myocardial depression and failure.

Fluid and Electrolyte Disturbances

Fluid and electrolyte disturbances could be marked particularly in patients who have sweated profusely. Hyperkalemia can be marked when heat stroke follows exercise or exertion particularly if there is rhabdomyolysis.

CLINICAL FEATURES[6]

The classic features of heat stroke are—

- A core temperature above 40°C often over 42°C. Temperature as high as 43–44°C (110°F) have been recorded.
- A disordered mental state which could vary from delirium, apathy, obtundation and coma.
- Elevated creatinine kinase present in most patients.
- A compatible historical setting.

Among other important but not necessarily constant features are seizures and anhidrosis in the presence of high core temperature. Absence of anhidrosis does not however negate the diagnosis. Ataxia, dysmetria, dysarthria with other cerebellar signs may be seen acutely and in survivors of heat stroke.

A careful examination often reveals dysfunction of all or most organ systems. Hypotension and cardiovascular collapse are frequent, forming the most common cause of death. Renal failure, metabolic acidosis, rhabdomyolysis, DIC and ARDS are all important complications. The cerebrospinal fluid (CSF) may show a rise in protein and some degree of pleocytosis often leading to a suspicion of meningitis. CSF culture is however normal.

PROGNOSIS

Heat stroke with core temperature at or over 42°C carries a high mortality. Cardiovascular collapse and DIC are very grave prognostic factors. A full blown DIC with bleeding in a patient with heat stroke is almost always fatal. Neurological sequelae are often present in survivors.

DIFFERENTIAL DIAGNOSIS[7]

In regions where malaria is endemic, the differential diagnosis of fulminant *Plasmodium falciparum* infection from heat stroke may be difficult or impossible without examining

a peripheral blood smear. In case of doubt particularly in zones highly endemic for malarial infection, treatment for *P. falciparum* infection should be empirically given. Acute pyogenic meningitis should be excluded by lumbar puncture. Other fulminant infections may be missed as heat stroke and vice versa. A blood culture should always be sent. It is important to stress that leukocytosis is fairly frequent in heat stroke so that its occurrence does not negate the diagnosis.

Rarely an Addisonian and also an acute thyroid crisis are associated with hyperpyrexia. Acute encephalitis or hypothalamic lesions can produce hyperpyrexia by upregulating the temperature set point. The temperature in hypothalamic lesions remains fixed and unvarying and the presence of associated lesions, in particular diabetes insipidus should help diagnosis. Imaging of the head should be done if there is suspicion of a CNS lesion.

Investigations with regard to all organ functions should be asked for and carefully monitored. A coagulation profile and a radiographic examination of the chest are of particular importance.

MANAGEMENT

The prime need is to reduce body temperature by heroic measures. If possible the patient is nursed in an air-conditioned room with the temperature of the room kept as low as the air-conditioner will allow. He or she should be covered in sheets soaked in very cold water, and a revolving fan is allowed to play on the body to further aid cooling. Rubbing ice on the body is not very effective but adding some alcohol to the cold bath water or in the water used to sponge the patient helps to increase heat loss from the body. An ice water enema is also useful to lower the temperature in hyperpyrexia. The head should be kept cool with ice on the head and with frequent ice cold compresses to the forehead. Oxygen should be given at 4–6 L/minute by a nasal catheter or a mask.

The reduction of body temperature by the above methods should be controlled by periodic checks of the rectal temperature. The ice bath or the cold sponge should be stopped when the rectal temperature reaches 102°F. A too sudden and drastic fall in temperature is uncommon, but should be avoided as it can cause sudden death.

A proper fluid and electrolyte balance should be maintained. Normal saline may be given particularly if there is history of excessive sweating prior to the stroke. All organ systems need to be meticulously supported. Hypotension should be countered by a volume load and by inotropes/vasopressors. The airway in unconscious patients should be secured and maintained. Clotting factors and platelets should be given to patients with DIC. Patients often need ventilator support. Renal replacement therapy should be offered to patients who have prolonged acute tubular necrosis. It should be noted the dantrolene is ineffective in heat stroke.[8] Unfortunately, there are no randomized clinical trials that have compared the effectiveness of different cooling methods in any hyperthermic syndrome.

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CHAPTER 70

Hypothermia

When the core temperature falls below 95°F (35°C), a patient is said to be hypothermic. Induced hypothermia is used by anesthetists to reduce cellular metabolism notably in heart surgery as also in other conditions as after resuscitation from cardiac arrest.

CAUSES OF HYPOTHERMIA[1]

Accidental hypothermia is due to exposure to cold (poverty in Asian countries and alcoholic stupor are two important background factors). Mountaineers and skiers who ski at high altitudes in inclement weather, hikers caught in rain and snow are situations where hypothermia poses real danger. Wet clothes aggravate the degree of hypothermia as does the presence of rain, wind and snow in freezing temperatures.[2,3] Deaths from complete immersion in cold water due to cold shock or inexorable hypothermia far exceed deaths from drowning without cold.

Urban hypothermia is particularly observed in old people, in destitutes who can afford neither proper clothing, nor shelter nor food. There are many in North India who die of cold in the winter months just as there are many who die of hyperthermia in the hot summer months in the Gangetic plains or in the tropical southern part of the country.

Fatigue worsens hypothermia as it decreases muscle glycogen stores, reduces heat production and reduces both the capacity to exercise and shivering.

Drugs[3,4] like phenothiazine, barbiturates and alcohol, frequently produce hypothermia in temperate or cold climates by depressing sensory afferents, the hypothalamus and efferent responses.

MEDICAL CONDITIONS

Hypothyroidism is the most important medical condition causing hypothermia. Myxedema coma is associated with subnormal temperatures in the vast majority of patients and has a high mortality unless treated with exogenous thyroid. Hypoglycemia and hyperosmolar nonketotic diabetic coma are also known to cause hypothermia.

CENTRAL NERVOUS SYSTEM DISORDERS

Strokes, tumors, Wernicke's encephalopathy or any pathology that can directly affect hypothalamic function have been known to be associated with hypothermia.

Skin disorders characterized by vasodilatation and increased transepithelial water loss may lead to hypothermia, as in extensive psoriasis, ichthyosis and erythroderma. Third degree burns are noted to have a huge evaporative heat loss, losing up to 6 liters of fluid and more than 3,400 kcal/day.

Trauma victims, particularly those with moderately elevated trauma severity scores, not uncommonly show hypothermia during the first few days of hospitalization.[5] The causes of hypothermia are listed in Box 1.

PATHOPHYSIOLOGY[6]

Profound metabolic changes occur in every organ system when the core temperature falls below 35°C. Temperature dependent metabolic changes occur in two phases. The shivering state usually occurs between 35°C and 30°C. Shivering is characterized by intense energy production from the breakdown of glycogen and other body fuels very similar

Box 1: Causes of unintentional hypothermia

- Old age
- Exposure to cold
- Drugs
- Myxedema, in particular myxedma coma, hypoglycemia
- CNS disorders involving the hypothalamus
- Skin disorders characterized by vasodilatation and excessive transepithelial water loss
- Trauma

to that observed in strenuous physical exercise. In the non-shivering phase the metabolism slows down markedly. All organ systems are affected, ultimately leading to multiple organ failure.

CLINICAL FEATURES[8]

Clinical features are related to the degree of hypothermia. At 34–36°C, hypothermic individuals are very conscious of being very uncomfortably cold. With a further fall in temperature, mental and physical problems increase; some victims are withdrawn and some become aggressive. At 33–34°C, victims often stagger, become confused and drowsy. Increasing bradycardia and hypotension are observed. Paradoxical undressing is sometimes observed because paradoxically there is a feeling of heat due to hypothalamic dysfunction causing an alteration in set-point temperature.

At 26–33°C, increased mental obtundation progressing to coma is observed. At 17–20°C, cardiac output is inadequate to sustain life. Death generally occurs from asystole or ventricular fibrillation. Nevertheless, it should be noted that successful resuscitation at core temperature well below 15°C has been reported.

COMPLICATIONS[6,7]

- After removal from a cold environment, there is often a further fall in core temperature for 10–20 minutes—the "after drop"; this might take the core temperature into the lethal zone.
- Arrhythmias particularly ventricular fibrillation are common. The ECG typically shows a J wave (junctional deflection at the junction of the QRS complex and the ST segment) and a prolonged QT interval.
- Metabolic acidosis.
- Pancreatitis.
- Rhabdomyolysis.
- Pneumonia.
- Sepsis.
- There is evidence of multiple organ dysfunction due to the effect of a low core temperature on the metabolism and function of all organ systems.

MANAGEMENT[6-8]

Management of the hypothermic victim is similar to that of any semiconscious or comatose patient. Immediate attention is focused on the *circulation, airway control breathing* and *rewarming*. Oxygen is promptly administered. Abnormalities in arterial pH; electrolytes corrected. The core temperature should be continuously monitored, preferably with a low reading rectal thermometer.

During rewarming, circulatory and respiratory support is essential. Blood volume should be expanded by infusion of normal saline or by a colloid infusion. Inotropic and vasopressor support is often necessary. A transvenous pacemaker is often required in the presence of severe bradycardia. Defibrillation of a hypothermic fibrillating heart is unlikely to succeed at a core temperature of less than 30°C.

If the respiration is very slow, irregular or shallow, the patient will need intubation and ventilator support.

Important complications other than cardiopulmonary failure include pancreatitis, rhabdomyolysis and pneumonia. The CPK should always be done; it may be over a thousand in the presence of rhabdomyolysis. Acute tubular necrosis is an important complication of the latter. Infection is common—in particular pneumonia—appropriate antibiotics are necessary. All organ functions need adequate support.

Rewarming of a hypothermic casualty needs to be done no sooner the patient has been rescued. A variety of rewarming methods are available. In milder cases, warm blankets and hot drinks suffice. Though commonly used, "metallized space blankets" are of no proven benefit. Warm intravenous fluids are helpful. In extreme cases peritoneal lavage with warm fluids, or if experience and expertise are available, cardiac bypass can also be used. Hot sponges or hot baths are effective but it should be remembered that they could cause a paradoxical fall in core temperature as blood flow is rapidly restored to cold extremities. As a general rule, if hypothermia in a victim has been prolonged in onset or duration, rewarming must be undertaken with extreme caution. In critical cases where rapid warming is needed, full resuscitation facilities must be at hand.

Pronouncement of death in patients with severe hypothermia should be made with great caution because of the marked bradycardia, marked respiratory depression and the very low stroke volumes present in these patients. It is best to warm the patient and then ensure that there is truly a cardiac arrest and that there is no respiration before pronouncing the patient's demise.

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SECTION

19

Critical Care of the Cancer Patient

- Critical Care of the Cancer Patient

CHAPTER 71

Critical Care of the Cancer Patient

GENERAL CONSIDERATIONS

The cure rate in cancer has increased over the last three decades. Patients with common cancers, like breast cancer, colorectal cancer and lung cancer, still defy a cure once these cancers have metastatized. There are however a number of cancers which can be cured even after metastasis. These include acute lymphatic or myeloid leukemia, chronic myeloid leukemia (after extensive radiation and allogenous bone marrow transplant), gestational choriocarcinoma, testicular tumors, Hodgkin's disease, aggressive non-Hodgkin's lymphomas, Wilm's tumor, Ewing's sarcoma and, in rare instances, small cell lung carcinoma. Survival of patients with other forms of metastatic cancers can also be extended for varying periods of time.

The definite increase in cancer cure rates is related to the development and use of new and more targeted therapeutic drugs. However, these drugs that have the potential to cure often lead to drug-related organ toxicities and increased susceptibility to infection. Many of these constitute acute life threatening complications that are potentially reversible and therefore unquestionably merit critical care. To give one example, the timely recognition and critical care of respiratory failure in cancer patients due to infectious, malignant or toxic complications is often extremely rewarding. Equally rewarding is the critical care management of systemic complications or syndromes directly related to cancer—for example, the tumor lysis syndrome and the hemophagocytic syndrome.

Though an acute, life-threatening reversible pathology in cancer patients does need critical care, the priority for such care is obviously low if the basic disease process is so advanced as to very sharply limit the expected life span. The priority increases and, in fact, admission to the intensive care unit (ICU) is imperative if the patient has a cancer which is either potentially curable, or which if effectively treated can result in an extended period of survival. However, therapeutic considerations in the ICU all over the world particularly in developing countries are being increasingly influenced by cost and outcome concerns. The intensivist, the treating physician or surgeon caring for a cancer patient faces the challenge in the ICU, to decide not only what should or can be done but also to decide if and when to do it, or whether to do anything at all.

POSTOPERATIVE CRITICAL CARE

In surgical ICUs, ICU admissions are related chiefly to immediate postoperative care after major surgery, or to surgical and other complications arising soon after massive surgery. Principles of surgical care are exactly the same as after major surgery unassociated with cancer.[1] The main postoperative support necessitating ICU stay is dependence on mechanical ventilation, especially over an extended period of time. Generally, the risks of untoward outcomes in the ICU correlate with the extent and magnitude of the surgical procedure. For example, ovarian cancer surgery involving resection of the gut, ventilatory dependency and hemodynamic instability requiring the use of a Swan-Ganz catheter, carries a higher morbidity and longer stay in the ICU. Considering the recent advances in surgery, postoperative risks are determined to a lesser extent by the technical aspects of the surgical procedure, than by existing comorbidity and general underlying factors that prevent an uncomplicated recovery.

Most surgical operations in cancer patients carry a procedure specific morbidity and mortality rate. Potentially lethal complications generally do not occur in the immediate or early postoperative phase, but later. Re-surgery (for whatever reason) carries a high morbidity and mortality. Postoperative

infection either in the surgical area or systemic infection is probably the greatest hazard, particularly in cancer patients who have received chemotherapy prior to surgery.

Critical care in cancer patients may be necessitated for several other reasons—

i. *Overwhelming or serious infection related to immunosuppression* (see Section The Immunocompromised Patient) Advanced malignancy is always associated with a reduction in immune response. Protein synthesis is abnormal, and continued rapid growth and spread of the tumor produces cachexia. Malnutrition worsens immunosuppression at this stage. A far more important cause of immunosuppression is related to severe neutropenia observed as a feature of acute myeloproliferative disease, or related to the use of chemotherapy and/or radiation. The more dose-intensive the chemotherapy or radiation therapy regime, the greater the likelihood of damage to host cells, and of severe thrombocytopenia and granulocytopenia. Immunosuppression often leads to acute infection which may be due to the usual micro-organisms infecting immunocompetent patients, or to opportunistic organisms. This has been dealt with in the Section The Immunocompromised Patient. Severe thrombocytopenia following radiation or chemotherapy may induce bleeding either within the skin and the mucosa, or in internal organs and other anatomical structures of the body.

ii. *Complications due to a mitotic lesion which can produce life-threatening emergencies* These complications can result directly from the tumor effects at the primary site or from spread of the tumor. Non-metastatic complications of malignant diseases can also result in serious problems meriting critical care.

iii. *Complications directly related to the side effects of antimitotic drugs or radiation (other than immunosuppression already mentioned above).*

Complications listed under (ii) and (iii) can best be considered in relation to different organ systems with specific reference to critical care requirements.

METABOLIC COMPLICATIONS AND SYSTEMIC CANCER-RELATED COMPLICATIONS OR SYNDROMES[2-5]

The systemic cancer-related complications or syndromes are the tumor lysis syndrome and the hemophagocytic syndrome. The main metabolic complications include hypocalcemia and hypercalcemia, hypophosphatemia, fluid and electrolyte disturbances, notably the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Tumor Lysis Syndrome[6-8]

This is particularly observed in rapidly proliferating tumors that are very sensitive to chemotherapy. The syndrome is classically associated with Burkitt's lymphoma, but in our part of the world it is most frequently observed during treatment of other malignancies.[9] These include acute lymphoblastic leukemia, chronic myeloid leukemia in an acute blast crisis, non-Hodgkin's lymphoma, and occasionally in small cell cancer of the lung, and metastatic breast cancer.

The syndrome is caused by rapid lysis of malignant cells resulting in hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and an increase in blood urea nitrogen. Though hyperuricemia and increase in uric acid excretion typically occur following chemotherapy in malignancy, these abnormalities can also occasionally occur in untreated patients with rapidly growing tumors.

Life-threatening complications include acute renal failure from precipitation of uric acid in renal tubules with uric acid nephropathy, and cardiac arrhythmias from hyperkalemia and hypocalcemia. Oliguria and azotemia are warning features; hypocalcemia can result in tetany, cramps and seizures.

Management[8]

Prevention consists of hydrating patients before and during chemotherapy, and using allopurinol 500 mg/m^2 per day for 3 days; this is reduced to 200 mg/m^2 per day after 3 days of chemotherapy. Chemotherapy is best instituted 24–48 hours after proper hydration and use of allopurinol. During chemotherapy, relevant blood biochemistry should be done every 12–24 hours.

Treatment

If metabolic aberrations are observed in the form of increasing hyperuricemia, oliguria and electrolyte abnormalities, as stated above, chemotherapy is either postponed or stopped. Allopurinol is given as above; the dose is decreased in the presence of renal insufficiency or if serum uric acid levels are controlled. Patients should be carefully hydrated, but in the presence of increasing oliguria, fluid overload should be watched for. Furosemide is given in a dose that maintains urine flow at over 100 mL/hour. An increase in urine output should be matched by an increase in oral and intravenous fluid intake. The urine should be alkalinized to a urine pH greater than or equal to 7 by the use of intravenous sodium bicarbonate. This is given in a dose of 75–100 mEq/L to start with, and subsequently the dose is adjusted to maintain an alkaline urine. Once the urine output increases and the serum uric acid falls, alkalinization of urine is no longer necessary. In patients who develop an acute renal shutdown, intravenous fluids are avoided for the purpose of hydration, else pulmonary edema occurs.

Hyperkalemia

Hyperkalemia needs urgent attention with 50% dextrose-insulin given intravenously, the use of intravenous bicarbonate and of an exchange resin sodium polystyrene sulfonate (see Section Fluid and Electrolyte Disturbances in the Critically Ill).

Hypocalcemia

Hypocalcemia is corrected by the use of 10% calcium gluconate intravenously, which can be repeated as and when necessary.

Hyperphosphatemia

Hyperphosphatemia is typically severe (serum levels ranging from 6 mg/dL to 35 mg/dL), and is due to both tumor lysis and increasing renal failure. It is treated with 20% dextrose-insulin till the phosphate levels are less than 6 mg/dL. Aluminum hydroxide 30–60 mL 6 hourly is given orally to bind phosphates in the gut. Good hydration, both orally and intravenously, helps excretion of phosphates via urine.

Some patients do not respond to the above therapy. They develop increasing oliguria and renal failure with hyperuricemia, persistent hyperkalemia and hyperphosphatemia. The criteria for starting dialysis are as follows—

- Serum uric acid levels higher than 10 mg/dL.
- Serum K^+ higher than 6 mEq/L.
- Serum phosphates higher than 10 mg/dL.
- Fluid overload.
- Symptomatic uncorrected hypocalcemia.

Hemophagocytic Syndrome[10]

The hemophagocytic syndrome has many underlying etiologies. An underlying lymphoma or cancer is an important cause of this syndrome which, if unrecognized and untreated, leads to almost certain death. It can also occur in infants and children as a primary event due to a genetic disorder. Secondary causes besides cancer and lymphoma also include viral infections and autoimmune disease.

It is characterized by high fever, splenomegaly, hepatic dysfunction, anemia, leucopenia, thrombocytopenia and hemophagocytosis, characterized by an enhanced macrophage and phagocytic activity which engulfs hemopoetic cells. It is caused by decreased lymphocyte killer T-cell activity; this results in a marked proliferation of lymphocytes and macrophages which infiltrate all organ systems and which produce various cytokines leading to multiple organ dysfunction and failure. Its laboratory markers are a sharp increase in serum ferritin (>10,000 µg/L), a sharp fall in fibrinogen levels and a marked increase in triglycerides. This syndrome requires expert critical care.

Treatment

Treatment consists of—

- Dexamethasone 100 mg/m^2 per day for the first 2 weeks; 5 mg/m^2 per day for the 3rd and 4th week; 2.5 kg/m^2 for the 5th and 6th week; 1.25 mg/m^2 for the 7th week tapering to zero over the 8th week.
- Etoposide 150 mg/m^2 intravenously twice weekly for the first 2 weeks; then once weekly for a total of 8 weeks.
- Methotrexate Intrathecal methotrexate and hydrocortisone are administered for four doses (weekly during weeks 3–6) only in the presence of neurological symptoms or a persistently abnormal cerebrospinal fluid (CSF).
- Supportive therapy Antimycotic therapy is given during the initial dexamethasone therapy. Trimethoprim 5 mg/kg is given thrice weekly as prophylaxis against pneumocystis.

Other Metabolic Problems in Malignancy

Syndrome of Inappropriate Secretion of Antidiuretic Hormone

The SIADH can cause mental obtundation, coma, seizures and even death. It occurs most frequently with a small cell lung cancer, but can occur with other malignant lesions as well. Besides being a non-metastatic complication of the tumor itself, SIADH can also result from chemotherapy, notably following the use of cyclophosphamide or vincristine. The treatment has been detailed in the Section Fluid and Electrolyte Disturbances in the Critically Ill. It is important to raise serum sodium gradually in these patients, so as to minimize the risk of central pontine myelinolysis.

Hypophosphatemia

Serum phosphate levels less than 3 mg/dL are occasionally observed with rapidly growing tumors and in severely malnourished cancer patients. The clinical features of hypophosphatemia are characterized by increased weakness which could also involve the respiratory muscles, poor myocardial function, as also leukocyte and platelet dysfunction. Phosphate levels less than 1 mg/dL can cause hemolysis and rhabdomyolysis. Treatment in an emergency consists of the administration of 30–40 mmoL/L of a neutral sodium or potassium phosphate solution at the rate of 50–100 mL/hour.

Hypercalcemia[11,12]

Hypercalcemia is the most common metabolic complication of malignancies, and one that most often requires critical care. It occurs in 10% of cancer patients[3] and, in some instances, constitutes a life-threatening emergency. It is most frequently associated with multiple myeloma, lung cancer, breast cancer, cancers involving the head and neck, T-cell lymphomas, renal carcinoma as well as other solid tumors. A rapid onset hypercalcemia can cause confusion, obtundation, psychosis and even coma. Vigorous hydration with intravenous normal saline combined with the use of furosemide is the standard therapy, and has been outlined in the Section Fluid and Electrolyte Disturbances in the Critically Ill. Corticosteroids, diphosphonates, mithramycin and calcitonin can all reduce serum calcium levels by reducing bone resorption of calcium. A combination of calcitonin and corticosteroids has the quickest effect in reducing serum calcium. Mithramycin has a good, but poorly sustained effect. Diphosphonates act slowly, but the effect is more sustained.

Table 1: Dosages of commonly used agents in the treatment of hypercalcemia

Drug	*Route of administration*	*Dosage*
Prednisolone	Oral	1–2 mg/kg per day
Salmon calcitonin*	Subcutaneous	100–400 u/6–12 hours
Mithramycin	Intravenous	25 µg/kg, once or twice per week
Diphosphonates (alendronate disodium)	Intravenous	7.5 mg/kg per day for 7 days

*Also used as a nasal spray.

Methods to counter hypercalcemia have been discussed in an earlier chapter, but for reasons of convenience, the dosage schedules of corticosteroids, calcitonin, diphosphonates and mithramycin are given in Table 1.

Hypocalcemia

Hypocalcemia in cancer can result from the following causes—

- Osteoblastic metastatic deposits in the bone from a prostate cancer or from a breast cancer on hormone therapy. Prostate cancer is the most common cause of hypocalcemia. More than 30% of patients with prostate cancer and extensive osteoblastic deposits develop hypocalcemia.
- The tumor lysis syndrome can result in hyperphosphatemia, with an increase in calcium phosphate product leading to deposition of calcium in various soft tissues. Hypocalcemia followed by the development of secondary hyperparathyrodism results.
- Low vitamin D_3 levels can also lead to hypocalcemia.
- Magnesium deficiency leads to hypocalcemia. This occurs in cancer patients on prolonged hyperalimentation when magnesium is not adequately replaced. It can also occur in patients on diuretics, in chronic diarrhea, in patients on cisplatin therapy and in those receiving intravenous phosphate. Both calcium and magnesium need to be given to correct hypocalcemia in these patients.

Clinical features have been described in the Section Fluid and Electrolyte Disturbances in the Critically Ill. They include tetany, muscle cramps, laryngeal spasm, headache, irritability and seizures. Chvostek's and Trousseau's signs are often positive and the electrocardiogram (ECG) shows a prolonged QT interval.

Treatment Treatment consists of intravenous administration of 10% calcium gluconate repeated after 20–30 minutes or as and when necessary. Magnesium in a dose of 1 g over 12–24 hours is given intravenously if there is an associated hypomagnesemia (<1.5 mg/dL).

Hyperglycemia

Hyperglycemia can occur in malignant disease without insulin deficiency. It has been reported in glucagonomas, somatostatinomas, and rarely in pheochromocytomas and adrenocorticotropic hormone (ACTH) secreting tumors. Nonketotic hyperosmolar hyperglycemic coma can occasionally result as a complication of cyclophosphamide, vincristine or prednisolone therapy, in patients who are mildly diabetic and in patients who are on intravenous alimentation. Hyperglycemia generally responds to treatment of the tumor either by resection, radiation therapy or chemotherapy.

Hypoglycemia

Hypoglycemia due to tumors is most frequently due to an insulinoma. However, an insulin-like substance causing severe persistent hypoglycemia can be secreted by some tumors. These include large retroperitoneal fibrosarcomas, mesotheliomas, and renal, adrenal and primary hepatocellular carcinoma. Extensive metastasis within the liver can also lead to hypoglycemia. Associated liver cell disease, hypopituitarism from any cause (including tumors) and myxoedema may also be responsible for hypoglycemia.

The immediate treatment is an intravenous infusion of 10–20% glucose to keep the blood glucose level higher than 60 mg/dL. Removal of the tumor whenever possible grants relief from hypoglycemia.

Hypokalemia Due to Ectopic ACTH Secretion

Besides adrenocortical tumors secreting cortisol and thereby producing Cushing's syndrome, a number of other tumors can secrete ectopic ACTH resulting in hypokalemia and Cushingoid features. These chiefly include small cell lung cancer, carcinoid tumors of the bronchi, cancers of the ovary, thyroid, and prostate, hematological malignancies and sarcomas.

The differential diagnosis of hypokalemia and potassium replacement in hypokalemia are both considered in the Section Fluid and Electrolyte Disturbances in the Critically Ill. Ideally, the effective treatment of hypokalemia and the induced Cushing's syndrome due to ectopic ACTH secretion is removal of the underlying tumor. If the tumor is unresectable chemotherapy should be tried.

HEMATOLOGICAL COMPLICATIONS[3]

The chief hematological complication requiring intensive care is bleeding. Bleeding may be directly related to a cancerous lesion in the gastrointestinal (GI) tract, or it may result from thrombocytopenia, or may be due to disseminated intravascular coagulopathy (DIC). Thrombocytopenia may result from neoplastic disease chiefly through infiltration of the bone marrow or could be drug induced. DIC can occur with a variety of cancers, but especially with promyelocytic leukemia, prostatic carcinoma, and cancer of the breast, lung

and the GI tract. Patients with DIC require transfusions with whole blood, packed cells, fresh frozen plasma and platelet infusions. Fibrinogenemia is countered by intravenous infusions of cryoprecipitate; 2–3 bags/10 kg body weight is infused initially, followed by 1 bag/15 kg body weight daily [see Chapter Transfusion (Blood Product) Therapy].

PULMONARY COMPLICATIONS[3]

Pulmonary complications in malignancies meriting critical care include—

- Acute respiratory failure.
- Central airways obstruction from tumor involvement of the upper airways or from pressure on the airway by mediastinal glands.
- Massive atelectasis of a lung due to endobronchial obstruction or to extrinsic pressure.
- Acute infections.
- Massive hemoptysis.

Acute Respiratory Failure

This most frequently results from lymphangitis carcinomatosis or alveolar cell carcinoma or widespread metastatic spread of cancer within the lungs. *These patients should be treated in the wards and not in critical care units.* In our opinion, they should not be ventilated; treatment is directed toward symptomatic relief. Acute respiratory failure could also result from complicating pneumonia, due to community acquired or nosocomial or opportunistic infection, or due to pulmonary embolism. These patients need expert critical care for survival.

Acute myeloblastic leukemia or chronic myeloid leukemia in a blast crisis can cause leukostasis with obstructed blood flow to small pulmonary blood vessels. This can lead to hypoxemic respiratory failure.

Respiratory failure may also result from treatment given to cancer patients.[13] A number of chemotherapeutic agents, in particular bleomycin and mitomycin, can cause pneumonitis with progressive pulmonary fibrosis and increasing hypoxemia.[13] Similarly radiation therapy can produce acute pneumonitis over a period of 6 or more weeks. Progressive fibrosis with respiratory failure can result due to a chronic radiation effect, particularly if large areas of the lung are irradiated or the patient has simultaneously received chemotherapy. It is believed that radiation injury to the lungs, with damage to the alveolar capillary wall produced by chemotherapy, is due to the formation of free oxygen radicals. The pathogenesis of lung injury in these patients is similar to oxygen toxicity produced by inhalation of very high oxygen concentrations (FiO_2), over a long period of time. Administering a high concentration of oxygen to these patients could conceivably increase the degree of lung injury, and may well produce irreversible lung damage. The lowest possible FiO_2 that can maintain an oxygen saturation of hemoglobin around 90% should therefore be used.

Central Airways Obstruction

Central airways obstruction from tumor involvement of the upper airways or by extrinsic pressure from mediastinal glands can produce asphyxia, and needs urgent surgical attention.

Massive Atelectasis

Massive atelectasis from endobronchial obstruction can cause acute respiratory failure. Temporary relief of the obstruction by therapeutic procedures performed via the bronchoscope may help.

Acute Infections

Acute leukemias, chronic myelogenous leukemia in blast crisis, Hodgkin's disease, malignant lymphomas and other malignant lesions are often treated with high dose chemotherapy. Radiation together with bone marrow transplants are also used in the treatment of leukemias. Patients with advanced breast cancer are also at times treated with very aggressive regimes. This causes prolonged severe neutropenia and thrombocytopenia. Bacterial, viral (particularly cytomegaloviral) and fungal infections can be fulminant and cause death in spite of vigorous antibiotic therapy and support. Cytomegaloviral pneumonia and diffuse interstitial pneumonia are dangerous complications following bone marrow transplants and carry a high mortality (see Section The Immunocompromised Patient).

Massive Hemoptysis

Hemoptysis can be severe in some patients with non-small cell lung cancers, and is particularly severe in squamous cell lung cancer. Intrapulmonary hemorrhage with hemoptysis can also occur in patients with severe thrombocytopenia; fluffy lung shadows with progressively increasing hypoxemic respiratory failure result.

CARDIOVASCULAR COMPLICATIONS

Cardiac Tamponade

Cardiac tamponade is an important complication that may necessitate critical care in patients with malignant disease. Tamponade is most frequently due to malignant pericardial effusion, but can be due to constrictive pericarditis arising from encasement of the heart by tumor tissue or to irradiation fibrosis.

Pericardiocentesis is urgently required to reverse hemodynamic abnormalities in malignant pericardial effusions. Surgical procedures by an experienced oncosurgeon may be necessary for long-term benefit.

Congestive Cardiomyopathy[3]

An extremely important cardiovascular complication in patients with mitotic disease is congestive cardiomyopathy,

induced by chemotherapeutic agents such as adriamycin or high dose cyclophosphamide. Progressive cardiac enlargement, increasing breathlessness, and pulmonary and systemic venous congestion can occur over a short period of 2–4 weeks, though in some patients the clinical features of heart failure may be delayed by a few months. A clinical follow-up, as also a follow-up by 2D echocardiography with specific reference to the ejection fraction, is of value in early diagnosis. Management consists of strict bed rest, the use of digitalis, diuretics and the use of angiotensin converting enzyme inhibitors to reduce the afterload. The incriminating drug should be avoided. Varying degrees of improvement in cardiac function may be observed with proper management.

SUPERIOR MEDIASTINAL SYNDROME[14]

The superior mediastinal syndrome most commonly results from a lymphoma or a metastatic carcinoma (chiefly from a carcinoma within the lung). However, the possibility of a benign cause for a superior mediastinal syndrome should always be kept in mind. For this reason it is wrong in principle to give chemotherapy or radiation to such a patient without a tissue diagnosis. In our part of the world, massive mediastinal adenopathy with a superior mediastinal pressure syndrome can result from tuberculous adenitis, particularly in the younger age group.

Patients with cancer, who have central venous catheters in situ, may develop superior vena caval thrombosis. This results in engorged neck veins and resembles a superior mediastinal pressure syndrome. An infusion of urokinase, through a catheter placed directly above the clot in the superior vena cava, often dissolves the clot and gives excellent relief. This is preferably followed by an intravenous infusion of heparin at a rate of 1,000 units/hour for 3–4 days. Long-term oral anticoagulation may be necessary in some patients.

Severe tracheal obstruction or obstruction to a large bronchus from a metastatic adenopathy due to cancer or lymphoma may need urgent relief. Stenting with a self-expanding metal endoprosthesis provides successful relief in 90% of patients. Chemotherapy is used in patients with small cell lung cancer, lymphoma and germ cell tumors. Radiation therapy is the only alternative for other cancers. It may temporarily increase upper airway obstruction, or further obstruct the superior vena cava, necessitating the insertion of a stent within the trachea and the superior vena cava.

GASTROINTESTINAL COMPLICATIONS[3]

Perforation of the gut may be a direct complication of a malignant lesion involving the GI tract. Perforation can also result from enterocolitis in neutropenic patients. Fever, diarrhea, abdominal pain and tenderness are present. The classical signs of acute abdomen after perforation may not be present in a severely neutropenic patient. Surgery is imperative, but the morbidity and mortality are high.

Severe GI bleeds, or localized intra-abdominal abscesses may also be serious enough to merit critical care in some patients.

Obstruction to the gut may be due to the disease process itself. Surgery, radiation therapy or intraperitoneal therapeutic interventions may however cause adhesions or damage to the gut, with resulting obstruction. It is often difficult to distinguish whether problems involving the gut are related to the malignancy per se or to therapy used against the disease. Expert surgical advice is imperative.

NEUROLOGICAL COMPLICATIONS[2,3]

Acute complications requiring critical care include increase in intracranial tension because of a primary tumor within the brain or due to metastasis within the brain.

Early diagnosis and prompt treatment of acute spinal cord compression due to metastatic disease or a primary neoplasm are of utmost importance. This requires a good clinical examination plus imaging studies. Cord compression diagnosed after myelopathy has already set in has the most unfortunate consequences on what remains of the patient's life—often a bedridden existence, with an indwelling catheter and with an increased risk of bedsores, pneumonia and urinary infection.

Once a clinical diagnosis of cord compression is made, the patient should be given pulsed doses of 1 g methylprednisolone for 3 days, as this helps reduce cord edema. Definitive neurosurgical treatment to decompress the cord should be prompt so as to avoid a permanent myelopathy.

Severe metabolic encephalopathy in a patient with malignant disease can be due to hyponatremia or hypercalcemia. Antimitotic drugs, like cytarabine, etoposide, methotrexate, ifosfamide, can also cause metabolic encephalopathy. Interleukin-2 (IL-2) and interferon-α can also cause somnolence and confusion. Paranoid psychosis, seizures and coma have been reported with IL-2. Management is chiefly symptomatic and supportive, and the offending drug should be promptly stopped.

ANTICANCER THERAPY REQUIRING INTENSIVE CARE

It is hardly ever necessary to give chemotherapy in an ICU setting. Recently however biological therapy chiefly with IL-2 is being increasingly administered under critical care conditions.[3] IL-2 therapy is particularly useful in patients with renal cell carcinoma and melanoma, the results being superior to other modalities of treatment. Other biological factors being used are the tumor necrosis factor (TNF) and interleukin-1 (IL-1). IL-2 is presumed to have a lymphokine-activated killer (LAK) cell activity.[3] An IL-2 regime however produces a predictable range of toxic effects which requires management in a critical care setting.[15-17]

IL-2 infusions can produce—

- Severe hypotension due to an increased vascular capacitance with a lowered systemic vascular resistance.
- Non-cardiogenic pulmonary edema.[3]

The hypotension is similar to that observed in septic shock, and is associated with a warm skin and a good pulse volume. Poor perfusion of organ systems results if the blood pressure is not raised. It is inadvisable to raise the blood pressure by a volume load, as this increases the tendency to produce non-cardiogenic pulmonary edema. It is best to raise the blood pressure by an infusion of phenylephrine 50 mg in 250 mL of 5% dextrose, the infusion being given at a rate of 20–40 μg/minute. If hypotension persists despite increasing doses of phenylephrine, the patient is given inotropic support either with dopamine or dobutamine. These patients invariably have a fair degree of left ventricular dysfunction. The deleterious cardiovascular effects of IL-2 are reversed within hours if the drug is discontinued. The drug can be restarted with a 25% reduction in dose, after the patient is hemodynamically stable.

The danger of non-cardiogenic pulmonary edema is minimized by restricting fluids and avoiding volume load. Hypoxia if present, is corrected by an appropriate increase in the FiO_2. If hypoxia persists with a hemoglobin oxygen saturation less than 90%, IL-2 is best omitted. It should be noted that the respiratory toxicity of IL-2 is not as easily reversed as the cardiovascular effects.

When LAK cells are infused together with IL-2, further complications include an additive effect on declining respiratory function, due to sludging of cells in the capillary bed. Bronchospasm and acute pulmonary edema have also been observed. Continuous positive pressure breathing or intubation with ventilatory support, may be necessary at times.

It is possible that in the decades to come, biological agents will be used with increasing frequency. The intensive care physician will therefore need to be aware of the potential grave complications, so that he can handle them successfully.

CONCLUSION

The survival rate of cancer patients requiring ICU admission has increased. It is imperative that potential salvageable life threatening emergencies in cancer patients are treated in critical care units. There are many reasons for improved survival of cancer patients in the ICU. They include quicker diagnosis and better treatment of acute respiratory failure, prevention of tumor lysis syndrome, earlier diagnosis and treatment of the hemophagocytic syndrome, better management of acute kidney injury, recognizing drug-related organ toxicities, advances in oncology, hematology and better over-all ICU care.[18]

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SECTION

20

Control of Pain and Anxiety and the Use of Muscle Relaxants in the Critically Ill Patient

- Control of Pain and Anxiety and the Use of Muscle Relaxants in the Critically Ill Patient

CHAPTER 72

Control of Pain and Anxiety and the Use of Muscle Relaxants in the Critically Ill Patient

INTRODUCTION

Pain is an important symptom of disease, and indiscriminate suppression of pain may delay diagnosis and prevent correct management. Once a diagnosis is made and effective treatment planned, pain must necessarily be relieved. Postoperative and post-traumatic pain also need effective relief as it serves no useful purpose and may prove detrimental to the patient in many ways.[1]

In the intensive care unit (ICU), pain management poses many challenges. Many critically ill people are incapable of communicating clearly, either due to their disease or injury or because of intubation and the need for sedation. Assessment and treatment of potentially painful conditions therefore become difficult. Also, there are many sources of pain that may be unrelated to their disease, but caused by procedures and therapies used to fight their disease. These sources of pain include for example surgeries, invasive procedures, and placement of monitoring devices, intubation and the use of dialysis to maintain renal function. An overall pain assessment in a conscious patient who can communicate requires a careful history into the nature, site and cause of discomfort or pain that is perceived. It is important to remember that a very strong overwhelming pain invariably suppresses lesser pains arising from one or many other sources. These may become evident when the cause of the very severe pain has been effectively dealt with.

DEFINITION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.

ANATOMY OF PAIN[2]

"For all the happiness mankind can gain is not in pleasure but relief of pain."

—John Dryden

Nociceptive stimuli are perceived by nerve endings throughout the body, and are conveyed by unmyelinated and small myelinated sensory axons to the posterior root ganglion in the spinal cord. A neuronal relay transmits the pain to the posterior horn cells. Many of the afferents terminating in the region of the spinal cord contain neuropeptides, including substance P. cholecystokinin and somatostatin. These peptides probably play an important role in sensory transmission. The spinal dorsal horn is divided into a series of layers. Neurones processing noxious or nociceptive stimuli are found in a number of these layers. Unmyelinated afferents terminate in substantia gelatinosa (Layer II), while the myelinated afferents end in Layers I and V. The axons of neurones arising from the dorsal horn cross to the opposite side to ascend upward as the ventrolateral spinothalamic tract. The spinothalamic tract can be conceptually divided into two systems based on its connections: (1) a direct tract ending in the ventrolateral nucleus of the thalamus, and (2) a phylogenetically older, spinoreticulothalamic tract that terminates at several levels within the reticular formation of the brainstem. This indirect tract is part of a polysynaptic system terminating in the medial thalamic nuclei.

Descending Analgesic Fibers[2]

In addition to this major ascending spinothalamic system, the nervous system contains descending nerve fibers that

suppress nociceptive inputs. These descending fibers (at least in animals) originate in the periaqueductal gray matter, synapse in the nucleus raphe magnus in the medulla, and then project downward into the spinal cord to the dorsal horns. The descending pathways can to an extent gate or restrict the initial nociceptive stimuli received in the dorsal horns. The descending analgesic pathways described above contain endogenous opiate peptides and opiate receptors. Opiate receptors are also present in the thalamus and the limbic system. These structures may therefore play an important role in the analgesic response to systemically administered narcotics.

Biogenic amines, like serotonin and norepinephrine, are other neurotransmitters also present in the fine terminals of the descending analgesic pathways. A major descending analgesic pathway originates in the nucleus locus coeruleus of the pons. This pathway contains norepinephrine and inhibits nociceptive responses within the posterior horns through an alpha-adrenergic mechanism.

PATHOPHYSIOLOGY OF PAIN[2]

Perception of pain within the neuraxis excites segmental and central responses. Segmental response is characterized chiefly by increase in muscle tension, which intensifies pain. The central response consists of an increase in sympathetic tone resulting in tachycardia, and a rise in both blood pressure and cardiac output. The metabolic rate and both oxygen demand and oxygen consumption may increase. Pain also excites a neuroendocrine response. There is an increased secretion of catecholamines, cortisol, adrenocorticotropic hormone (ACTH), aldosterone, antidiuretic hormone, glucagon and an increase in the production of a large number of cytokines. Insulin secretion can decrease. Severe unrelieved pain increases the catabolic state, and may cause a negative nitrogen balance; this could result in decreased immune function and delay wound healing. Nociceptive stimuli if unrelieved can result in insomnia, nausea, vomiting, ileus, prolonged immobility and a feeling of increasing anxiety, distress and frustration in the patient. Unabated chest pain as after cardiothoracic surgery can also contribute to poor respiration, through restriction of movements of the chest wall and diaphragm. This increases the chances of postoperative atelectasis. Pain may contribute to immune dysfunction, hypercoagulable states, increase in blood glucose levels and patient-ventilator asynchrony. It robs the patient of rest and sleep and indirectly retards the healing process in a critically ill individual.[3] Management of pain and anxiety is therefore a vital aspect of critical care.

The following section first describes the use of both narcotic and non-narcotic drugs for analgesia in a critical care setting. It then discusses the use of anxiolytic and sedative agents in critically ill individuals, and ends with a brief description of muscle relaxants in the ICU.

USE OF OPIOIDS OR NARCOTIC ANALGESICS FOR PAIN RELIEF[4]

Opioid or narcotic analgesics are the drugs most frequently used to relieve pain in critical care units. They may be used alone or in combination with non-steroidal anti-inflammatory agents. Remarkably enough, analgesics are often overused or underused. Their administration should be guided by the background disease, the immediate cause and the severity of pain. The dose should always be individualized and titrated as needed. Pain relief must always be balanced against potential side effects of narcotics (chiefly respiratory depression, hypotension), and the effect these side effects could produce on the overall clinical outcome in a gravely ill individual.

Opioids (narcotic analgesics) can be given orally, intramuscularly or intravenously. Over the last 20 years, new delivery systems have been developed, so that opioids can also be administered by the epidural, intrathecal, transdermal and transmucosal routes. Opioids produce both analgesia and sedation through their action on the opioid receptors of the central nervous system.

The intramuscular route of administering narcotic drugs is universally accepted for pain relief. We prefer to administer the drug as and when needed; the drug could also be given at fixed intervals (at 4–6 hours), provided the patient is carefully monitored. The major advantage of the intramuscular use of opioids is a lesser incidence of respiratory depression and hypotension, when compared to intravenous (IV) use. The disadvantage is a comparatively erratic absorption, erratic blood levels and slower action.[4]

Relief of severe pain in a critical care setting is quicker and easier with a titrated IV administration of a narcotic analgesic.

INTRAVENOUS NARCOTIC ANALGESICS[5]

The IV administration of narcotics brings prompt relief of pain and anxiety in an ICU setting. The dosage and the exact method of IV administration (either by bolus injections or by a continuous IV infusion) need to be individualized for each patient. Morphine (5 mg) or buprenorphine (0.1–0.3 mg) given in a very slow IV bolus dose affords quick relief from pain. If IV morphine is given at intermittent intervals, the dose is 0.03 mg/kg every 10–20 minutes, care being taken to ensure that respiration is not unduly depressed, and hypotension does not occur. Naloxone can reverse the respiratory depressant effect of morphine. A smaller dose of 2 mg morphine or 0.1 mg of buprenorphine should be initially given in elderly or frail patients so as to note the effect on respiration and circulation. Morphine fortunately is a little more easily available in India (though it requires a permit) compared to the difficulty obtaining it a few years ago. When unavailable, ICUs make do with buprenorphine in its place.

Morphine or buprenorphine can also be given in a continuous IV infusion. An infusion rate of 0.5–1.5 mg/hour

of morphine, or 0.01 mg/kg per hour of buprenorphine, allows a steady level of the narcotic within the blood, and offers good relief. Alternatively, 0.5–1 mg/kg together with 50 mg promethazine is added to 100 mL of 5% dextrose saline, and given intravenously in an infusion over 30–40 minutes. Here again, respiratory depressant and hypotensive side effects of the narcotic should be watched for. The patient ideally should remain sedated and free of pain, but yet easily arousable.

Hydromorphone (Dilaudid) is frequently used in the West for its potent analgesic effect. It is unavailable in our country, except through a special permit. When used intermittently, the recommended dose is 10–30 µg/kg intravenously at 2 hourly intervals. The infusion dose ranges 7–15 µg/kg per hour.

OTHER SYNTHETIC NARCOTIC-ANALGESICS

Pentazocine

Pentazocine belongs to the benzomorphan group of synthetic compounds. It is indicated in the treatment of pain of intermediate severity. Around 30 mg of pentazocine is equivalent to 10 mg of morphine. The drug can be given intramuscularly, by intermittent IV injection, or in an IV infusion in the dose stated earlier. Its main advantage is that it does not cause dependence unless used in high doses for prolonged periods. Unlike pure narcotic agonists, its effects cannot be reversed by nalorphine. IV naloxone is an effective antidote.

Pethidine (Meperidine)

Pethidine is similar to morphine, but has a shorter duration of action, and is less potent in relieving pain. It is usually administered in a dose of 1 mg/kg intravenously. Its use is contraindicated in patients who are on monoamine oxidase (MAO) inhibitors. Pethidine is metabolized by the liver; a principal product of metabolism is norpethidine, which can cause tremors, apprehension, delirium and seizures, and may interact with antidepressants.

Fentanyl

Fentanyl is a recent synthetic opioid which is 50–100 times more potent for pain relief compared to morphine. The IV dose for an adult weighing 60–70 kg is 1–2 µg/kg. The drug has a short duration of action and has no significant effect on the circulatory system. It is increasingly used both in general anesthesia and as a potent analgesic. Though fentanyl is the quickest and shortest acting analgesic, repeated doses may cause accumulation and prolonged effects. When administered as an IV infusion, the dose is 0.2–0.5 µg/kg per hour.

In patients with lesser degree of pain, fentanyl can be applied transdermally as a patch. The subdermis acts as a reservoir from which a slow and steady absorption of the drug occurs. Patches can deliver 25 µg/hour, 50 µg/hour, 75 µg/hour and 100 µg/hour. Peak analgesic levels occur after a time lag of 10–12 hours. A careful watch on possible respiratory depression and hypotension should be kept. Transdermal fentanyl should not be used for severe pain where need for urgent analgesic relief is important.

Remifentanil

Remifentanil is even quicker and shorter acting than fentanyl, as it has a half-life of 3–10 minutes. It is given in an infusion in a dose of 0.6–15 µg/kg per hour. The short action and quick arousal after discontinuing the drug is useful when frequent clinical and, in particular, neurological assessment is called for.

Butorphanol Tartrate

Butorphanol tartrate is a recent opioid analgesic now available in India. It has a short half-life and is seven times more potent than morphine. When given intravenously, its peak action is within 0.5–1 hour and its duration is 3–4 hours. The IV dose is 1 mg repeated every 3–4 hours. Depressant effects on respiration and circulation need to be carefully watched for.

Ketamine

Ketamine is a potent analgesic and anesthetic. It is chiefly used in the ICU for bedside procedures and has been discussed in a later section of this chapter.

PATIENT CONTROLLED ANALGESIA[4,6,7]

Patient controlled analgesia (PCA) permits self-administration of a preset quantity of a narcotic intravenously, as and when needed. PCA enables a patient to control his own analgesic requirements. A lockout device is incorporated into the system to prevent overdosage of the narcotic. This method provides effective analgesia, effective control over pain and anxiety, improves pulmonary function in postoperative patients, reduces sleep disturbances, and is shown to reduce the overall drug requirement, when compared to other methods of narcotic administration. The dosage in PCA needs to be individualized. An example of a prescribed dosage schedule with morphine is as follows: 2–5 mg as a loading dose over 15–30 minutes, followed by a patient triggered bolus of 1–2 mg via the PCA pump, programmed with a lockout interval of 15 minutes. This schedule may be changed according to the patient's response.

A similar schedule for morphine is as follows: 0.3–0.5 mg as a loading dose, followed by 0.1–0.2 mg of a patient triggered bolus via the PCA pump, with a lockout interval of 15 minutes.

The PCA method of pain control can be combined with a slow infusion of a narcotic which allows a steady blood level of the drug to exert a continuous analgesic effect. It is essential to check the respiration, basic circulatory parameters, and the level of mental obtundation when using this combined approach to the relief of pain.

Caution is required in the use of continuous infusion of opioids in critically ill patients, as these patients have altered and fluctuating volume status, altered protein binding capacity and may have renal and/or hepatic dysfunction.

RECOMMENDATIONS FOR ANALGESIA IN ICU PATIENTS

It is important that the intensivist familiarizes himself with just a few opioid (narcotic) analgesics. The clinical practice guidelines on the use of analgesics in the critically ill adult have the following recommendations to make on analgesia[5]—

- A therapeutic plan and goal of analgesia should be established for each patient.
- If IV doses of an opioid analgesic are required, fentanyl, remifentanil and morphine are recommended agents. In our country where morphine is difficult to obtain, buprenorphine could substitute for morphine.
- Scheduled opioid doses or a continuous infusion is preferred over an "as needed" regime for consistent analgesia. In our opinion this may hold for a certain group or category of patients, and "as needed" approach is safer and almost as effective.
- Fentanyl or remifentanil is preferred for a rapid onset of analgesia in acutely distressed patients.
- Fentanyl or hydromorphone (not available in India) is preferred for patients with hemodynamic instability or renal failure.
- Morphine (buprenorphine is a substitute) is preferred in intermittent therapy because of its longer duration of effect.

ADVERSE EFFECTS OF OPIOIDS

The following are the adverse effects seen with the use of opioids—

- Depression of respiration. This needs to be carefully watched, particularly in the old and feeble.
- Hypotension, due to a sympatholytic effect and a vagally mediated bradycardia.
- Marked depression of the conscious level, which interferes with clinical assessment.
- Rarely hallucinations and agitation are observed.
- Gastric hypomotility, ileus, urinary retention, constipation occur particularly with prolonged or frequent administration; these require symptomatic treatment.
- Increase in intracranial pressure has been reported in patients with head injury.

It should be noted that tolerance to the drug over time is observed with all opiates. Synthetic opioids like fentanyl exhibit tolerance more quickly than the non-synthetic ones, because of their higher receptor affinity. Rapid withdrawal or de-escalation of an opioid can cause withdrawal effects with resulting delirium which may be wrongly attributed to other causes.

EPIDURAL AND INTRATHECAL OPIOIDS[8,9]

Epidural anesthesia is extremely useful for relief of pain following orthopedic, thoracic or vascular procedures. It also helps to improve postoperative outcomes in high-risk patients as manifested by a reduced incidence of postoperative thromboembolism, myocardial infarction and by improvement in pulmonary and bowel functions.[9] A Cochrane review comparing epidural to systemic opioid technique for pain relief showed that epidural analgesia was superior. It was also associated with reduced cardiovascular, gastrointestinal and renal complications, and with reduced time on ventilator support. Epidural analgesia using opioids is extremely useful not only for pain relief but also for reduced morbidity and mortality in patients with multiple (>4) rib fractures following trauma to the chest.

Epidural and intrathecal administration of opioids relieves pain by acting on spinal pain receptors. Epidural administration of a narcotic is much more frequently used. It produces good relief with a relatively small quantity of the drug, without blocking motor and sympathetic nerves. It requires the placement of a catheter in the epidural space. Morphine and buprenorphine are the most frequently used analgesic narcotics. Since buprenorphine is more easily available, 150 μg of the drug diluted in 10–20 mL of N-saline is administered slowly. This provides pain relief that may last for 12–16 hours, after which the dose can be repeated. Pethidine can also be used epidurally in a similar fashion, for pain relief.

Morphine and buprenorphine have been shown to spread in a cephalic direction to reach the fourth ventricle, after epidural administration. Two phases of respiratory depression may be observed. The first phase occurs within 30–45 minutes, and reflects absorption of the drug into the blood via the epidural veins. The second phase of depression occurs after 6–8 hours, and occasionally as long as after 24 hours; it is due to rostral spread of the drug into the fourth ventricle, causing a direct depressant effect on the respiratory center. Most patients become sedated before developing respiratory depression. An increasing sedative effect should be watched for, as it precedes respiratory depression. It is best to avoid the systemic administration of narcotics if the epidural route is being used, as the danger of serious respiratory depression significantly increases.

Fentanyl, like morphine, is a lipophilic agent which travels rostrally when given intrathecally or through a catheter placed in the lumbar epidural space. It however travels in a cephalad direction less slowly than morphine, and is not as effective as the latter for relief of thoracic pain, but has fewer side effects.[10,11]

Epidural administration of narcotic analgesics can be given in the bolus form, as a continuous infusion (using an infusion pump), or can be administered as an infusion that can be controlled by the patient, as per his/her requirements (PCA).

SPINAL ANESTHESIA

Spinal anesthesia through intrathecal techniques is used for operative and immediate postoperative pain control. This mode is not used for pain control in ICU patients because of increased risk of complications. Intrathecal administration of

opioids leads to a much higher cerebrospinal concentration of the drug when compared to epidural administration. The risk of severe respiratory depression and hypotension is therefore considerably enhanced.

REGIONAL ANESTHESIA[4]

Regional blocks to relieve pain are also of considerable use in certain circumstances. A typical example is the use of a regional intercostal block to relieve pain and ease breathing in a patient with rib fractures. Brachial plexus blocks can relieve severe pain in the upper limb, and local infiltration of a wound area in suitable cases can relieve pain arising from a serious wound. Regional anesthesia blocks both afferent and efferent pathways of the reflex arc, and minimizes metabolic and neuroendocrine responses to painful stimuli. However, when local anesthetics are used intrathecally, care must be taken to minimize side effects. These include hypotension and limb weakness or even paralysis secondary to sympathetic and somatic nerve block.

Lidocaine 1–2% is the most commonly used local anesthetic in the ICU, because of its rapid action lasting for a significant period of time, and its low incidence of side effects. It is used locally prior to the insertion of central lines and the pulmonary artery catheter. It is also used topically (in 4% strength) in the nose, mouth, throat, tracheobronchial tree, esophagus and urethra. An uncommon but important side effect following the local use of lidocaine is a hypersensitivity reaction that can rarely cause anaphylaxis. Lidocaine is also used to provide pain control in spinal, epidural, caudal, nerve and field blocks.

Bupivacaine 0.25% is used in obstetric anesthesia. It is slow-acting, but produces marked analgesia for a prolonged duration of time. It is often used for epidural anesthesia and for intercostal nerve blocks (Table 1).

Table 1: Types, indications and considerations for regional blocks in the intensive care unit

Types of blocks	*Indications*	*Special considerations*
Thoracic epidural	Thoracic surgery, chronic pancreatitis, upper abdominal surgery, rib fractures	Epidural hematoma or abscess Accidental intrathecal puncture Hypotension from sympathetic blockade
Lumbar epidural	Trauma, lower extremity surgery	Same as above
Femoral or sciatic block	Lower extremity pain (thigh, knee, leg)	Positioning difficulties with sciatic block
Intercostal block	Rib fracture, chest tube insertion	Pneumothorax, empyema
Phrenic nerve block	Upper extremity pain, trauma, surgery	

Source: Adapted with permission from Fishman SM, Ballantyne JC, Rathmell JP (Eds). Bonica's Management of Pain, 4th edition. Philadelphia: Lippincott, Williams and Wilkins; 2010. pp. 1589, 1596.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS[4]

These drugs act by exerting an inhibitory effect on prostaglandin synthesis. Non-steroidal anti-inflammatory drugs include diclofenac sodium (50 mg 8 hourly intramuscularly or orally), and piroxicam (40 mg daily intramuscularly or orally). These drugs can relieve mild to moderate pain, but do not have the same efficacy observed with the narcotic group of drugs in the relief of severe pain. They often cause gastritis, acute upper gastrointestinal (GI) erosions, occasionally ulceration in the small or large gut which can bleed profusely, platelet dysfunction, and interstitial nephritis leading to renal dysfunction. Elderly patients with hypovolemia or hypoperfusion, and those with pre-existing renal insufficiency are more prone to non-steroidal anti-inflammatory drug (NSAID)-induced renal failure.

A number of oral NSAIDs are available, which include ibuprofen and naproxen. More selective COX-2 inhibitors are also available for oral administration. They are believed to produce less gastric irritation on long-term use. Acetaminophen is also useful to relieve mild pain. NSAIDs can on occasions be combined with the use of opioids for pain relief, so that the dose requirement of opioids is reduced.

A valuable addition to the non-steroidal anti-inflammatory drugs is ketorolac tromethamine, which can be given intramuscularly or intravenously for pain relief.[4] This drug has no direct effect on opiate receptors. It is a potent analgesic—30–90 mg given intramuscularly has an efficacy comparable to 10 mg of morphine. The dose should be halved in elderly patients, and the drug should preferably not be used for more than 5 days for fear of inducing renal insufficiency. Ketorolac is non-addicting and does not depress respiration. Its side effects are similar to those of other non-steroidal anti-inflammatory drugs. It should be avoided in patients with renal dysfunction, or in patients with a bleeding tendency.

We prefer as far as possible to avoid the use of non-steroidal anti-inflammatory drugs in critically ill patients. Oral or IV paracetamol is used for relief of mild pain and opioids for relief of more severe pain as indicated earlier.

Table 2 lists commonly used opioid and non-opioid analgesic drugs in a critical care setting.

ANALGESICS AND ANESTHESIA FOR BEDSIDE PROCEDURES[4,12]

Cardioversion

Diazepam (5–10 mg) or midazolam (2–3 mg) given intravenously is a safe and effective premedication prior to cardioversion, provided of course that there is sufficient time to use the premedication. Diazepam offers sedation, hypnosis and a period of amnesia.

Table 2: Common analgesic drugs used in the ICU

Drug	*Equianalgesic dose IV (mg)*	*Intermittent dose*	*Infusion dose*	*Main adverse effects*
Morphine	10	0.03 mg/kg IV every 15–20 minutes	0.02–0.07 mg/kg per hour	Depressed respiration, hypotension
Buprenorphine	0.3	3 µg/kg	0.01 mg/kg per hour	Same as above
Fentanyl	200	0.35–1.5 µg/kg IV at 0.5–1 hour	0.7–10 µg/kg per hour	Same as above Rigidity with high doses
Pentazocine	50	0.5–1 mg/kg		Depressed respiration, hypotension
Pethidine (Meperidine)	75–100	Not recommended	Not recommended	Same as above Occasionally excitability, tremors, delirium, seizures
Hydromorphone (not available in India)	1.5	10–30 mg/kg per hour	7–15 µg/kg per hour	Depressed respiration, hypotension
Ketorolac		15–30 mg intramuscular (IM) every 6 hours Decreased in elderly patients Avoid in renal insufficiency Do not use >5 days		Platelet dysfunction, Gastrointestinal bleed, renal dysfunction

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BEDSIDE DEBRIDEMENT OF WOUNDS, OTHER MINOR SURGICAL PROCEDURES IN THE ICU, OR EXCISION OF ESCHAR IN BURNS PATIENTS

Ketamine is a phencyclidine anesthetic which produces dissociative anesthesia, hypnosis and analgesia. It is also an N-methyl-D-aspartate (NMDA) receptor antagonist. When given intravenously in a dose of 2 mg/kg, it acts within 30–60 seconds. Its effect is short-lasting, and it has a plasma half-life of 2–3 hours.[13] This excellent anesthetic allows minor bedside surgical procedures like debridement of painful wounds, to be performed in the ICU. The drug when used intravenously as a short acting anesthetic is also extremely useful in the care of burns patients, particularly for the excision of eschars. Ketamine can also be given intramuscularly in a dose of 5–10 mg/kg, its onset of action then being 3–8 minutes. Ketamine in a dose of 1–2 mg/kg produces analgesia, with little change in the level of consciousness; the degree of analgesia is equivalent to that obtained with opioids. In the ICU, ketamine can be given before intubation, prior to changing a surgical dressing, prior to orthopedic manipulations and for other surgical procedures, such as incision, drainage of an abscess, or a tracheostomy.

The short anesthesia induced by intravenously administered ketamine (provided it is given slowly over 1 minute) is associated with preserved gag and laryngeal reflexes, and a slightly increased skeletal muscle tone. Ventilation is generally not depressed, and the patient does not require to be intubated. Emergence from anesthesia may be associated with excitement and hallucinations, which can be easily controlled by diazepam, or droperidol. Stimulation of the cardiovascular system may result in tachycardia and mild hypertension. Ketamine may induce profuse salivation, and hence an antisialogogue should be administered prophylactically.

ANXIETY, AGITATION AND THE USE OF SEDATIVES IN THE CRITICALLY ILL PATIENTS[14-17]

Anxiety is a feeling of nervousness and apprehension. Agitation is a sense of anxiety plus irritability, restlessness, marked arousal so that rest and sleep are either difficult or impossible.

The ICU is to an extent a hostile environment for critically ill patients. Noxious stimuli include pain, noise, suctioning of oropharyngeal and tracheal secretions, or tragedy involving other patients in the unit. Added to this is the sense of isolation, the difficulty encountered in communication (particularly in patients with an artificial airway), physical restraints associated with immobilization, other distressing sensory inputs, fear, anxiety and often deprivation of sleep. All these features can lead to a stressful situation, eliciting a mental response that ranges from anxiety and depression, to anger, hostility, agitation or even psychosis.

Sedative-hypnotic medications are often necessary to calm the patient and dull the edge of anxiety and fear. The agents most frequently used are the benzodiazepines. Occasionally, propofol and barbiturates are also used; narcotics should preferably be given only for pain, or when pain and anxiety coexist. The present discussion is restricted to the use of benzodiazepines. Ideally, a sedative and anxiolytic agent used in the ICU should have the following features—rapid onset of action, effective response, predictable duration of action, no adverse effects on vital functions, in particular on the respiratory and cardiovascular functions, and ease of administration. The drug should have a good therapeutic index, and, if possible, a specific antagonist should be

Table 3: Richmond Agitation-Sedation Scale (RASS)

+4	Combative	Combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tubes or catheters; aggressive
+2	Agitated	Frequent non-purposeful movement; fights ventilator
+1	Restless	Anxious, apprehensive, but movements not aggressive or vigorous
0	Alert & calm	
−1	Drowsy	Not fully alert, but has sustained (>10 sec) awakening (eye opening/contact) to voice
−2	Light sedation	Drowsy, briefly (<10 sec) awakens to voice or physical stimulation
−3	Moderate sedation	Movement or eye opening (but no eye contact) to voice
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Source: Adapted from Sessler CN, Gosnell MS, Grapp MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166:1338-44; and from Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale [RASS]. JAMA. 2003;289:2983-91.

available in case of overdosage. Benzodiazepines satisfy many of the above requirements. They have sedative and anxiolytic effects, produce muscle relaxation, and have anticonvulsant properties.

The ideal level of sedation is one where the patient sleeps, yet is easily arousable. Severely hypoxic patients on mechanical ventilation or those on neuromuscular paralytic agents may require a higher degree of sedation.

MONITORING SEDATION

No subjective or objective method or technique is ideal for monitoring sedation. Several monitoring protocols have been devised. The Riker Sedation-Agitation Scale (SAS) has proved satisfactory for ICU patients.[18] The Vancouver Interaction and Calmness Scale is also used, and in children a widely used scale is the COMFORT scale.[19] A monitoring scale used in the ICU should be simple, yet should document the degree of anxiety present and the degree of sedation achieved with accuracy.

The Richmond Agitation Sedative Scale (RASS) is discussed in Table 3.

The RASS is a 10-point scale with criteria to distinguish levels of agitation and sedation; it takes very little time to complete. It has been shown that—

- The use of sedation target (i.e. level of desired sedation) through a protocol-based therapy reduces both patient anxiety, agitation, and improves patient outcome.[20,21]
- Daily interruption of sedation should always be part of the protocol to allow careful patient assessment.
- Patient awakening (through interruption of sedation) should be linked with spontaneous breathing trial, if a decision to wean the patient off ventilator support has been made. This has been shown to reduce time on ventilator support and reduce ICU and hospital stay.[22,23]

DIAZEPAM

Diazepam is the most commonly used drug. It binds to specific receptors in the hypothalamic, thalamic and limbic areas of the brain (responsible for sedative effect), and to spinal receptors in the spinal cord, enhancing the inhibitory effects of gamma aminobutyric acid (GABA) and other inhibitory neurotransmitters (responsible for a muscle relaxant effect). An IV dose acts within 1 minute, the maximum effect being observed in 2–5 minutes, and the duration of sedative action lasts for 4–6 hours. The drug is metabolized in the liver by microsomal oxidation and demethylation, its active ingredients being excreted by the kidneys. The drug should preferably not be given intramuscularly as its absorption is then erratic.

Diazepam is chiefly used as an anxiolytic agent which produces sedation and anterograde amnesia for stressful events. It is also used as a muscle relaxant (as in tetanus), and as an anticonvulsant (as in tetanus and in status epilepticus). It is the premedication of choice for cardioversion and for endoscopic procedures, and is also used in the management of addictive drug or alcohol withdrawal.

It is usually given slowly intravenously as a 2–10 mg bolus, and repeated after 6–8 hours, if necessary. For cardioversion, 5–10 mg is given intravenously 5 minutes before the procedure. Status epilepticus is managed by 10 mg bolus doses of IV diazepam, or by an infusion of 30–50 mg of the drug in 500 mL of N-saline. It is important to remember that individual response to the drug varies greatly, so that the dose should always be titrated to the response, particularly in feeble patients, or in the elderly.

Diazepam can produce prolonged drowsiness and impairment of intellectual and psychomotor functions. Respiratory depression and even apnea may occur, particularly if given rapidly. Bradycardia, hypotension, and even cardiac arrest have occurred in patients who are exquisitely sensitive to the drug, or when a large rapid bolus injection is used. The drug should be used with great caution and, as far as possible avoided altogether in patients with liver or renal dysfunction. Milder forms of anxiety are best treated by the oral use of the drug, 5–10 mg thrice daily.

LORAZEPAM

Lorazepam is a benzodiazepine with no specific advantage over diazepam. It acts on the benzodiazepine receptors in the central nervous system and spinal cord, enhancing the function of the inhibitory neurotransmitter GABA, by promoting the binding of this neurotransmitter to its receptors.

It has the same sedative, anxiolytic, muscle relaxant and anticonvulsant properties as diazepam. The duration of action is 6–10 hours, and is longer than that observed with diazepam. The usual IV dose is 0.04 mg/kg. The maximum dose that can be administered is 2 mg intravenously and 4 mg intramuscularly. The bioavailability on intramuscular injection is better and more predictable than with diazepam. The dose however as with diazepam needs to be titrated and individualized depending on the response. In status epilepticus, the drug is given in a dose of 0.1 mg/kg IV up to 4 mg per dose. The dose may be repeated every 10 minutes till seizures stop. It can also be given as a slow infusion of 4–8 mg/hour in 500 mL of normal saline. Currently lorazepam is preferred to valium in the management of status epilepticus.

The side effects are exactly similar to those observed with diazepam. However, venous thrombosis is infrequent with the use of lorazepam.

MIDAZOLAM

The main advantage of this drug over diazepam is its very short duration of action. It is also two to three times more potent than diazepam. On IV use, its action starts within 1 minute, peaks in 5 minutes, and lasts for 30–120 minutes. The drug has a short plasma half-life of 1.5–3 hours. Its metabolism is through mitochondrial oxidation in the liver, and its half-life (as with the other benzodiazepines) is significantly prolonged in liver cell dysfunction.

It is effective both intravenously and intramuscularly in a dose of 0.1 mg/kg, to a maximum of 2.5 mg/kg. Intermittent doses of 2.5–5 mg can be given every 3–4 hours. The drug in some instances can also be given as a slow IV infusion at the rate of 0.5–5 µg/kg per minute. The drug is freely available for use and it appears to have become the benzodiazepine of choice in many ICUs in the West. Its indications are exactly the same as for diazepam, and it has the same side effects. Apnea and severe respiratory depression may occur, particularly in old, feeble patients. Myocardial depression and hypotension are also observed particularly in hypovolemic patients who have received narcotics. A careful watch should be kept on cardiovascular and respiratory function, following its use.

Clinical features of overdosage with benzodiazepines are not uncommon in critical care units. This effect is either due to extreme sensitivity to the drug, or to overuse of the drug. Respiratory depression and hypotension can be life-threatening in some critically ill patients. Flumazenil is the specific antidote for benzodiazepines, and may be given slowly intravenously in a dose of 1 mg. The dose can be repeated up to a total dose of 3 mg.

PROPOFOL (DI-ISOPROPYLPHENOL)

Propofol is both an IV sedative and anesthetic. It is short-acting and rapidly metabolized. When used as sedation, an initial IV dose of 0.5–1 mg/kg is given, followed by an infusion of 25–70 µg/kg per minute. The infusion rate is titrated to the level of sedation required. Patients become awake within 20 minutes of the discontinuation of the drug. The shortness of action and quick arousal after stopping the drug are very similar to that of midazolam.

Propofol comes as a lipid emulsion and strict aseptic technique in administration should be followed for fear of nosocomial infection.

Side effects include hypotension, vasodilation. Sudden death has been reported from metabolic acidosis, particularly in children.[24] Myoclonic jerks have been observed in some patients after drug withdrawal.

BUTYREPHENONES

These drugs inhibit dopamine-mediated neurotransmission in the cerebrum and basal ganglia, resulting in an improvement in abnormal thought patterns; a detachment of the patient from the environment is observed. Haloperidol (the most commonly used butyrephenone) is a useful drug to calm agitated patients. The drug is given parenterally in a dose of 0.5–5 mg; it takes 30 minutes for a full response to be evident. The drug could be repeated if agitation is uncontrolled or recurs. A small maintenance dose at night for 5–7 days may prevent night-time delirium or hallucinations.

Side effects include extrapyramidal signs, dyskinesia and very rarely the neuroleptic malignant syndrome. The drug also causes a prolongation of the QT interval; an electrocardiograph should therefore be monitored, particularly in cardiac patients.

DROPERIDOL

Droperidol is similar to haloperidol but has a greater antiemetic and sedative effect than the latter. It can be combined with opioids to enhance sedation without causing further respiratory depression.

DEXMEDETOMIDINE

Dexmedetomidine is a selective α_2 agonist approved for short-term use in patients receiving mechanical ventilation. It has both analgesic and anxiolytic properties, maintaining easy arousability as well. Side effects include bradycardia and hypotension.

BARBITURATES

They are one of the oldest of sedative hypnotic drugs. They are used chiefly as sedative hypnotics and as anticonvulsants in patients with seizures.

Table 4 lists the IV dose, onset of action, peak action, and duration of action of the commonly used sedatives.

MUSCLE RELAXANTS IN INTENSIVE CARE[25]

Neuromuscular blocking agents are often used in critical care units. They are absolutely indispensable in the management

Table 4: Intravenous dosages, onset of action, peak action and duration of action of commonly used sedatives in the ICU

Drug	*IV Dose*	*Onset of action (min)*	*Peak action (min)*	*Duration of action*
Diazepam	2–10 mg	1–2	2–5	4–6 hours
Lorazepam	0.04 mg/kg	1–5	60–90	6–10 hours
Midazolam	0.1 mg/kg	1–2	2–5	0.5–2 hours
Propofol	1–2.5 mg/kg (maintenance dose 50–150 µg/kg/min)	<1	1–2	5–10 mins
Haloperidol	0.15 mg/kg*	1–5	60–90	4–8 hours

*IM dose

of severe tetanus, and following major neurosurgery, or a head injury where restlessness, agitation and straining are to be controlled, and where sedation is contraindicated for various reasons. Neuroparalytic agents are also indicated in status epilepticus which is uncontrolled or poorly controlled with the usual sedatives and antiepileptics. Mechanical ventilator support is mandatory in patients receiving neuroparalytic agents.

Perhaps the most frequent use of neuroparalytic agents in the ICU is to help in mechanical ventilator support in patients who continue to clash severely with the machine. In such instances, effective ventilation becomes impossible. Neuroparalytic agents should however only be used if all obvious correctable causes of a clash between the patient and the machine are carefully excluded. These causes have been discussed in the Chapter Mechanical Ventilation in the Critically Ill, and include incorrect ventilator settings, hypoxia, alveolar hypoventilation, a blocked airway, pneumothorax, airways obstruction and a decreased compliance of the lungs due to edema, pneumonia or atelectasis. There are however a number of patients where asynchrony between the patient and the ventilator is due to either uncontrolled agitation, or to a strong respiratory drive. The latter is most frequently observed in severe intrinsic lung disease (as in acute lung injury), and can only be abolished by the use of muscle relaxants. The use of inverse ratio mechanical ventilation in acute lung injury also often necessitates the use of muscle relaxants for proper ventilator support. Sedation, and relief of discomfort, pain and agitation with diazepam or narcotics, often enables the physician to offer ventilator support, without ultimately resorting to neuroparalytic drugs.

A patient paralyzed by a neuroparalytic agent has a feeling of extreme helplessness and dependency which leads to fear and anxiety. The use of benzodiazepines as sedatives and anxiolytic agents is mandatory in all such patients, as also the use of an analgesic for pain relief.

DEPOLARIZING AGENTS

Succinylcholine

This is the only clinically available depolarizing neuromuscular blocking agent. On IV administration it acts within 60 seconds, and has a short duration of action (5–10 minutes). It acts by binding to postsynaptic cholinergic receptors causing persistent depolarization and muscle paralysis. The drug however stimulates all cholinergic receptors, including autonomic ganglia, post-cholinergic nerve endings, and cholinergic receptors in the vessel walls.

The following side effects can be observed with succinylcholine—

- Bradycardia sometimes leading to sinus arrest. This is usually seen after administration of a single large bolus dose, or following a second dose of the drug, given approximately 5 minutes after the first dose.
- Persistent muscle fasciculation. This can cause a hyperkalemia which at times can lead to arrhythmias. Hyperkalemia is enhanced in burns, following trauma, crush injuries, and following cerebrovascular accidents. Succinylcholine is therefore best avoided in these conditions.
- Malignant hyperthermia can be triggered following its use.
- A rise in intragastric pressure, which could cause regurgitation of gastric contents, and aspiration pneumonia.
- Increase in intraocular pressure.

The main use of succinylcholine in a critical care setting is to permit endotracheal intubation, when clenching of the jaw or increased muscle tone makes laryngoscopy impossible. The dose used is 1–2 mg/kg intravenously.

NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

These agents bind competitively to the postsynaptic cholinergic receptors at the neuromuscular junction, and prevent depolarization of the muscle by acetylcholine. They thereby induce a paralytic state in all voluntary muscles. The drugs chiefly in use are pancuronium, atracurium, vecuronium and rocuronium.

Pancuronium

This is the main neuroparalytic agent easily available in poor countries. It is a long-acting water-soluble, steroidal non-depolarizing agent which is excreted mainly by the kidneys (90%). Its renal clearance depends on the glomerular filtration rate. The drug is also metabolized and broken down into less active metabolites in the liver (10%).

It is administered in a bolus dose of 2–6 mg intravenously (0.06–0.08 mg/kg). Muscle relaxation is observed in 3–4 minutes, and lasts for 40–120 minutes. The intubating dose is 0.08–0.12 mg/kg. Besides its neuroparalytic effect,

pancuronium causes histamine release and has a mild vagolytic effect. It is unnecessary to aim for complete or total paralysis with this drug. The dosage should be titrated in such a manner as to enable the physician to achieve his objective. This does not always necessitate total paralysis. The drug can also be given as a continuous infusion through an infusion pump. We prefer the bolus method because it allows constant easy assessment of the patient, and in our opinion, a better titration of the dosage and frequency of administration of the drug, particularly when used over a long period of time.

Pancuronium in clinical practice has little effect on the cardiovascular system. However, after prolonged use (as in severe tetanus), each bolus dose may be followed by a transient drop in blood pressure due to histamine release. The elimination half-life of the drug is 90–160 minutes, and this is significantly prolonged in patients with hepatic or renal dysfunction. The dosage should be suitably reduced and carefully titrated in these conditions, else it can result in prolonged paralysis.

We have used this drug in patients with severe tetanus for as long as 6–8 weeks, with comparatively few or no side effects.

Atracurium

Atracurium is a non-depolarizing neuromuscular blocking agent, benzylisoquinolinium that has an intermediate duration of action. Renal or hepatic dysfunction does not prolong its half-life; the drug is therefore safer to use when compared to pancuronium in renal or hepatic disease.

The IV dose in adults is 0.5 mg/kg. The onset of action is within 2 minutes, peak action occurs in 3 minutes, and the total duration of action is 20–60 minutes. IV administration should be slow; a rapid bolus can cause significant histamine release and hypotension. It can be given by continuous infusion at a rate of 0.3–0.6 mg/kg per hour; in most instances, recovery is rapid once the infusion is stopped. It is recommended for prolonged neuromuscular paralysis as in tetanus. It is however more expensive than pancuronium.

Vecuronium

Vecuronium is an intermediate acting monoquarternary analog of pancuronium. Its great advantage is that it provokes no histamine release, has no vagolytic effects, and its use is therefore associated with a very stable cardiovascular system. The drug is chiefly metabolized by the liver, and is partially excreted by the kidneys.

In adults, the drug is administered intravenously in a dose of 0.1 mg/kg. Its action starts within 2 minutes, peaks in 3–5 minutes, and duration of action lasts for 20–30 minutes. A continuous infusion of the drug is recommended in patients needing prolonged paralysis. The dose needs to be suitably reduced in patients with hepatic or renal dysfunction. Patients with cardiac disease do not require any adjustment in dosage. In patients with hepatic or renal disease, the duration of its effect may be variable and unpredictable.

Rocuronium

Rocuronium is an intermediate acting steroidal neuromuscular blocking agent. The intubating dose is 0.6–0.8 mg/kg and the duration of action is between 20–40 minutes. It is primarily eliminated by the liver and it is very useful in hemodynamically unstable patients in the ICU.

OTHER NON-DEPOLARIZING NEUROPARALYTIC AGENTS[4]

These include doxacurium, pipecuronium, mivacurium and cisatracurium. Doxacurium and pipecuronium resemble pancuronium, but do not affect the cardiovascular system. Mivacurium has the shortest duration of action, its effect lasting for just 15–20 minutes. We have no experience with these drugs.

COMPLICATIONS FOLLOWING THE USE OF MUSCLE RELAXANTS

Total or near total paralysis can induce fright and panic, hence the imperative need to use sedatives and anxiolytic agents in patients who are given muscle relaxants.

Pulmonary Complications

Paralyzed patients cannot cough. Secretions need to be carefully aspirated through the endotracheal tube or tracheostomy. Suction is often used in conjunction with expert physiotherapy to prevent atelectasis from retained secretions.

Neuromuscular Dysfunction

Delayed recovery from induced paralysis and neuromuscular dysfunction can occur after prolonged use of muscle relaxants.[26] The following clinical syndromes are observed.

The first is a myopathy producing the clinical picture of flaccid quadriparesis. It is typically observed in severe asthmatics receiving high dose corticosteroids and who have been given muscle relaxants during ventilator support. Flaccid paralysis, increased creatinine kinase levels in blood, myonecrosis and slow recovery that can take several months characterize the clinical picture. Pancuronium, atracurium, vecuronium have all been reported to produce this syndrome. Steroid dose and the dose of muscle relaxants should be kept to a minimum. The creatinine kinase level in the blood should be monitored and if the concentration increases, the muscle relaxant should as far as possible be stopped. The incidence of myopathy in asthmatics on both steroids and muscle relaxants, in our experience is between 10% and 20%; the higher the dose of these drugs the greater the risk.

The second syndrome is a motor neuropathy without myopathy, following the long-term use of vecuronium and pancuronium. The neuropathy involves both upper and lower limbs, producing weakness, wasting of muscles and absent

Box 1: Complications associated with the use of muscle relaxants

1. Ventilator failure or circuit disconnection can cause disaster if not promptly recognized
2. Pulmonary complications—
   - Inability to cough—atelectasis
   - Pulmonary infection
   - Retained secretions—atelectasis
3. Prolonged paralysis after stopping muscle relaxant—
   - Persistent neuromuscular blockade
   - Steroid-associated myopathy
   - Motor neuropathy
   - Neuromuscular dysfunction
   - A combination of the above
4. Immobility—
   - Pressure sores
   - Peripheral nerve injuries
   - Deep venous thrombosis
   - Pulmonary embolism

tendon reflexes. Weaning from mechanical ventilation is delayed and recovery may take weeks or even months.

A third syndrome observed following prolonged use of pancuronium or vecuronium is motor weakness of the limbs which on an electromyography (EMG) is related to failed neuromuscular transmission. Recovery occurs over several months.

Finally, a mixed neuromyopathic syndrome may be observed. Notwithstanding the above description, we have been singularly fortunate in using pancuronium for prolonged periods of time in severe tetanus, without significant side effects.

Many sophisticated ICUs find it helpful to titrate the requirement and dose of muscle relaxants by the use of a peripheral nerve stimulator, with assessment of train-of-four (TOF) responses.[27] This is a luxury we have dispensed with. Clinical judgment invariably suffices in adjusting both the dose and the frequency of administration.

Box 1 lists the common complications associated with the use of muscle relaxants in the ICU.

REVERSAL OF NEUROMUSCULAR BLOCKADE

Depolarizing agents have no specific antagonists. Neuromuscular block caused by non-depolarizing drugs can be reversed by anticholinesterase drugs. The drugs commonly used are neostigmine (0.06 mg/kg), pyridostigmine (0.2 mg/kg) and edrophonium (0.5 mg/kg). Atropine (0.01 mg/kg) is given simultaneously to counter the muscarinic side effects of these anticholinesterase drugs.

Sudanimex is a new antagonist of drugs causing nondepolarizing blockade. It is the first selective relaxant binding agent. It produces rapid and effective reversal of even more profound rocuronium induced muscular blockade. Sudanimex is ineffective against succinylcholine and benzylisoquinolinium, neuromuscular blockers such as atracurium, mivacurium and cisatracurium.

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SECTION

21

Critical Care of the Transplant Patient

- Critical Care of the Transplant Patient

CHAPTER 73

Critical Care of the Transplant Patient

INTRODUCTION

Organ transplantation is an increasingly prevalent form of management in end-organ disease. Renal transplant, heart transplant, lung transplant, heart and lung transplant, liver transplant, and pancreas transplant are the solid organ transplants being practiced in large centers in all Western countries, as also in a few countries in the East. In India, many centers have been carrying out renal transplants for several years. Liver transplants are being performed in special centers in Delhi, Chennai and Hyderabad with results as good as those reported in the West. Mumbai lags behind, but hopefully will do better in the next few years. Heart transplants, heart and lung transplants, and single lung transplants, barring isolated exceptions are unfortunately not being done on an organized scale. There is hope that they too will slowly start to increase in numbers in the years to come. Stem cell transplantation is in a way slightly different from solid organ transplants, and is also being done in few centers in the country.

The reason for organ transplant surgery not keeping pace with countries in the West is twofold. Earlier on, the law in our country did not legally recognize brain death, thereby sharply reducing the donation of heart, lungs, liver and pancreas for transplant purposes. Fortunately, good sense dawned on our lawmakers, and by an act of parliament, brain death has been accepted as a legal definition of death since 1994. There is also a lack of social awareness of the need to donate organs under the right circumstances to save lives. This social awareness has unfortunately yet to be cultivated in our country. The infrastructure and organization necessary for the use of cadaver transplants in India is being increasingly better organized. It is to be ardently hoped that ethical safeguards for donor organs are strictly formulated and followed.

This chapter gives an overview of the critical care of patients receiving solid organ transplants. It deals only with the principles of renal, liver and single lung transplant postoperative care. We have no experience with critical care of patients with heart or both heart and lung transplants. We have included some basic features of critical care of lung transplant recipients because there was one successful lung transplant done at the Hinduja Hospital in Mumbai, and there is hope that more will follow. Even so, there are basic problems common to all solid organ transplant surgeries. These are briefly dealt with below.

There are three major groups of complications in organ transplantation that determine outcome.[1] These complications are common to all solid organ transplants. They include—

1. Technical complications resulting from the surgical procedure of the graft implant and other postoperative complications.
2. Complications due to the effect of immunosuppressive therapy, to poor graft function, or to rejection of the graft.
3. Complications due to infection.[2]

Technical problems are generally observed in the early postoperative period, within the first 10–12 days. Rejection primarily occurs later between 10 and 60 days or even later. Side effects of immunosuppressive drugs can occur early or late. Infectious complications can occur any time after transplant surgery, due to active suppression of the immune system. However, the pattern of infection in these patients in the early postoperative period (1–30 days) is different from the pattern observed in the period from 1 month to 4 months or even later.

Not all patients with organ transplantation require critical care. Renal transplants are not routinely managed

in the intensive care unit (ICU), unless age, background disease or complications discussed below necessitate close monitoring or critical care management. On the other hand, heart transplant, heart and lung transplant, lung transplant, liver transplant and pancreas transplant, all need critical care for a varying period of time after surgery. Many patients may also require critical care in the pre-transplant period for a varying length of time. A preoperative assessment in all potential transplant recipients begins with a proper history, physical examination, electrocardiography (ECG), X-ray chest, a full biochemical and blood profile, and also blood and tissue typing. Patients with evidence of coronary artery disease undergo a more thorough cardiac evaluation, which includes a two-dimensional (2D) echocardiography, and when indicated, a coronary angiography. Critical lesions in the coronaries should be preferably corrected before performing, for example, a renal transplant. Similarly, endoscopy is indicated if there is a history suggestive of peptic ulcer, and transplant surgery is delayed till the ulcer has healed. The assessment of compliance is an important preoperative feature of organ transplant surgery. A work-up prior to transplant surgery includes a study of Hepatitis B and C viral (HBV and HCV) markers, other viral titers, which should include antibodies for the cytomegalovirus (CMV) both in the recipient and donor, tests for human immunodeficiency virus I (HIV I) and HIV II, urine culture, and cultures of a throat swab.

General contraindications for transplant surgery include malignancy, sepsis, manifest HIV infection which has not been correctly treated, history of drug abuse, hepatitis, noncompliance and advanced disease in an organ system, other than the one being considered for transplant.

IMMEDIATE POSTOPERATIVE CARE

The postoperative management of a transplant patient follows the general principles of postoperative care with special reference to monitoring functions of the organ transplanted. Heart, lung and liver transplants will require mechanical ventilation for at least 24 hours. Nasogastric suction through a nasogastric tube is required for intra-abdominal transplants and in patients on ventilator support. Enteral feeds are started as soon as gut function returns.

The emphasis on laboratory data or on other investigational procedures will depend on the organ transplant that has been done. Serial chest X-rays are important in the early postoperative period to assess the lung fields, and to check the placement of various lines and tubes. Common prophylactic measures include the use of antacids or sucralfate to protect against stress ulcers and the ulcerogenic effect of corticosteroids. Parenteral antibiotics in very good units are chiefly used perioperatively for adequate antibacterial cover. Many units in the West use antifungal agents for oral *Candida* prophylaxis, trimethoprim-sulfamethoxazole for prophylaxis against *Pneumocystis carinii,*[3] and ganciclovir for the first 3 months to prevent CMV infection in solid organ transplants. Immunosuppressive therapy is a mandatory postoperative feature of all organ transplant regimes.

CRITICAL CARE IN KIDNEY TRANSPLANT RECIPIENTS

The transplanted kidney is usually placed extraperitoneally in the recipient's right or left iliac fossa with end-to-side anastomosis to the external iliac vessels. It can however also be placed intraperitoneally either in the right or left iliac fossa. The transplanted ureter is reimplanted into the recipient's bladder in a manner to prevent ureteric reflux. Though most patients after renal transplant surgery are managed in the wards, complications arising after surgery may need critical care. The complications may occur in the immediate postoperative period (1–10 days) or a little later (10 days to 1 month) or later still (1–6 months or more). These have been briefly discussed below.

COMPLICATIONS OF RENAL TRANSPLANT SURGERY[3-5]

Urological Complications[6]

Improvement in surgical techniques has sharply reduced the incidence of postoperative urological complications. Currently urological complication rates are 4–8% with a very low mortality rate.

- Urine leaks and urinomas are rare complications and occur during the first few postoperative days (technical problems) or, at the most, in the first few weeks (ureteric necrosis). Extravasation of urine may occur from the renal pelvis, but more often occurs from the ureter at the ureteroneocystostomy site due to ureteric necrosis caused by vascular insufficiency, or to increased urinary pressure caused by obstruction.

Urinomas are usually found between the transplanted kidney and the bladder; they may however occur in unexpected sites as in the labia or the scrotum. A significant urinary leak leads to a decrease in urine output and a wrong diagnosis of graft failure may be entertained. Clinical signs include fullness and tenderness around the graft, swelling of the ipsilateral leg, or scrotal or labial edema.

On ultrasonography, a urine leak appears as a well-defined anechoic fluid collection, which is observed to increase in size fairly rapidly. Drainage of the urinomas with ultrasonographic guidance and estimation of the creatinine content of the fluid proves the diagnosis. Computed tomography (CT) scans, nephroscintigraphy and retrograde cystography are other investigative modes that can prove and outline the extent of a urinary leak.

Minor leaks may spontaneously resolve with Foley's catheter decompression. Recipients with large leaks in the early postoperative period are best explored with reimplantation of the ureter into the bladder.

Large urinomas may rupture to produce urinary ascites, or get infected to form an abscess. A urinoma may also track upward through pores in the diaphragm into the right pleural space.

- Mild hematuria from the distal ureter or the cystostomy is often seen in the immediate postoperative phase, but generally stops within 12–24 hours. Hematuria may, however, lead to a clot formation in the bladder, which in turn can lead to an obstructive uropathy with well-nigh cessation of urine output. Obstructive uropathy is the most common cause of new onset anuria in the immediate postoperative period and should be promptly treated with catheter irrigation. If anuria persists, a Doppler ultrasound should be done to ensure patency of the renal artery and vein, and also rule out a large hematoma causing an obstructive uropathy.
- Hematomas and lymphoceles are early post-transplant complications. They can cause an obstructive uropathy or can compress the iliac veins leading to leg edema and venous thrombosis.
- Ureteric stenosis is a late complication occurring months after transplant. Ureteric stenosis may be secondary to rejection, infection, ischemia or a tight ureterocystostomy. Hydronephrosis is present and detected on ultrasonography. A percutaneous nephrostomy helps to elucidate the location and degree of the ureteric stenosis. A balloon dilatation and placement of a temporary stent generally solves the problem.

Vascular Surgical Complications Leading to Graft Dysfunction and Failure[6]

Vascular complications are surgical complications and occur in the early postoperative period, at times even in the immediate postoperative period. They include vascular thrombosis either involving the renal artery or renal vein. The incidence of vascular thrombosis is from 0.7% to 5%, but it always results in a loss of the graft. The striking clinical feature of *renal artery thrombosis* is a sudden fall in urine output and rise in creatinine. Salvage is only possible if the vascular thrombosis is discovered within the first few hours. If several hours have elapsed, salvage is unlikely and a nephrectomy of the transplant becomes necessary.

Renal artery stenosis can result from the presence of intimal flaps, preimplantation arterial or graft damage, size discrepancy between donor and recipient vessels and hypotension or hypoperfusion during surgery.

Renal vein thrombosis can be caused by kinking of the anastomosis, injury, pressure on the veins due to fluid collection (urinoma, hematoma and lymphocele) or may occur as an extension of iliofemoral vein thrombosis. It usually occurs within the first few days after transplant surgery. It is characterized by the sudden onset of pain, swelling over the graft, hematuria, and if due to extension of an iliofemoral vein thrombosis, it is associated with swelling and edema of the lower limb. A Doppler ultrasound reveals a pulsatile renal artery with reversal of blood flow surrounded

by a hematoma. If thrombosis of the renal vein is total, a nephrectomy is necessary. If the thrombosis is incomplete, a successful thrombectomy may save the graft. As an alternative, thrombolysis with urokinase or treatment with heparin is recommended.

Early Graft Dysfunction

Medical problems that can lead to early graft dysfunction are acute tubular necrosis (ATN), acute rejection and recurrence of kidney disease.

Acute tubular necrosis[4] Acute tubular necrosis is the most common cause of impaired renal function in the immediate postoperative period. It may be observed immediately after revascularization or may have a slightly delayed onset. ATN may last from several days to as long as 6 weeks. The most frequent cause of ATN is prolonged ischemia to the graft. Donor factors, such as age, hypertension, use of vasopressors during procurement of the graft or during the transplant surgery may also contribute to the complication. Ischemia, ischemia-reperfusion injury, drug nephrotoxicity and acute infection are other factors that could precipitate ATN. It has a detrimental effect on later graft function, overall graft survival and on postoperative morbidity.[7] Measures to prevent graft rejection in this early period include volume expansion, avoidance of nephrotoxic drugs and minimizing calcineurin inhibitors during the peritransplantation period. If delayed graft function persists, a biopsy of the transplant kidney is performed within the first 3 weeks of transplantation.

The differential diagnosis of ATN is from other causes of acute oliguria or anuria. The most important differential diagnosis is renal artery or renal vein thrombosis. A Doppler ultrasound can easily establish the integrity of the circulation and blood flow through the renal artery and vein.

Hemodialysis needs to be continued in patients with ATN till such time as graft function recovers. Recovery occurs in over 95% of recipients. If delayed graft function persists, a biopsy of the transplant kidney is performed within the first 3 weeks of transplantation.

Acute or hyperacute rejection of the graft Acute or hyperacute rejection of the graft though rare does occur. Acute antibody-mediated rejection leads to a quick decline in early graft function. It is caused by allo- and autoantibodies formed in the recipient following pregnancy or following blood transfusions received earlier by the recipient because of an earlier organ transplant. These preformed antibodies can target capillary endothelium, activate complement resulting in a quick destruction of the graft. Only a biopsy of the graft can confirm the diagnosis, which should be followed by a surgical removal of the graft. A detailed description of the acute rejection syndrome is outside the scope of this book.

Recurrence of kidney disease[8,9] Acute kidney diseases do not generally recur. Focal segmental glomerulosclerosis (FSGS) can however recur and cause severe early graft dysfunction. Proteinuria more than 3.5/day in a recipient with known FSGS should prompt biopsy of the graft.[8] Similarly, a hemolytic uremic syndrome (HUS) can recur in a transplant kidney or it may even occur de novo in a transplant kidney. The use of tacrolimus, cyclosporine (calcineurin inhibitor) has been implicated when the HUS occurs de novo.[9]

Later Graft Dysfunction-Rejection

Though acute or hyperacute rejection of the renal transplant can occur within the first 10 days, it is much more frequently observed between 10 days and 1 month of surgery. In fact, rejection leading to graft dysfunction is the major complication in this period. There are, however, other important causes of graft dysfunction and it is vital to determine whether the dysfunction is related to rejection or to other causes. Oliguria following a renal transplant can be due to different etiologies. A careful and quick diagnostic evaluation should distinguish between rejection and other causes so that correct management can be promptly instituted. A diagnostic work-up of oliguria after renal transplant surgery is given in Flowchart 1.

A confirmed diagnosis of rejection is best made on histological grounds. An early histological diagnosis of rejection can lead to a suitable modification of immunosuppressive therapy and result in improved graft survival. However, in some renal transplant centers, a diagnostic biopsy is not performed before the first treatment for rejection with corticosteroids. Most centers do a diagnostic biopsy before a second course of treatment or before using antilymphocytic preparations. In renal transplant patients, cyclosporine therapy can unfortunately cause renal dysfunction indistinguishable from renal dysfunction induced by rejection. The need for a kidney biopsy and its correct interpretation helps to distinguish between these two important causes of poor function of a renal graft.

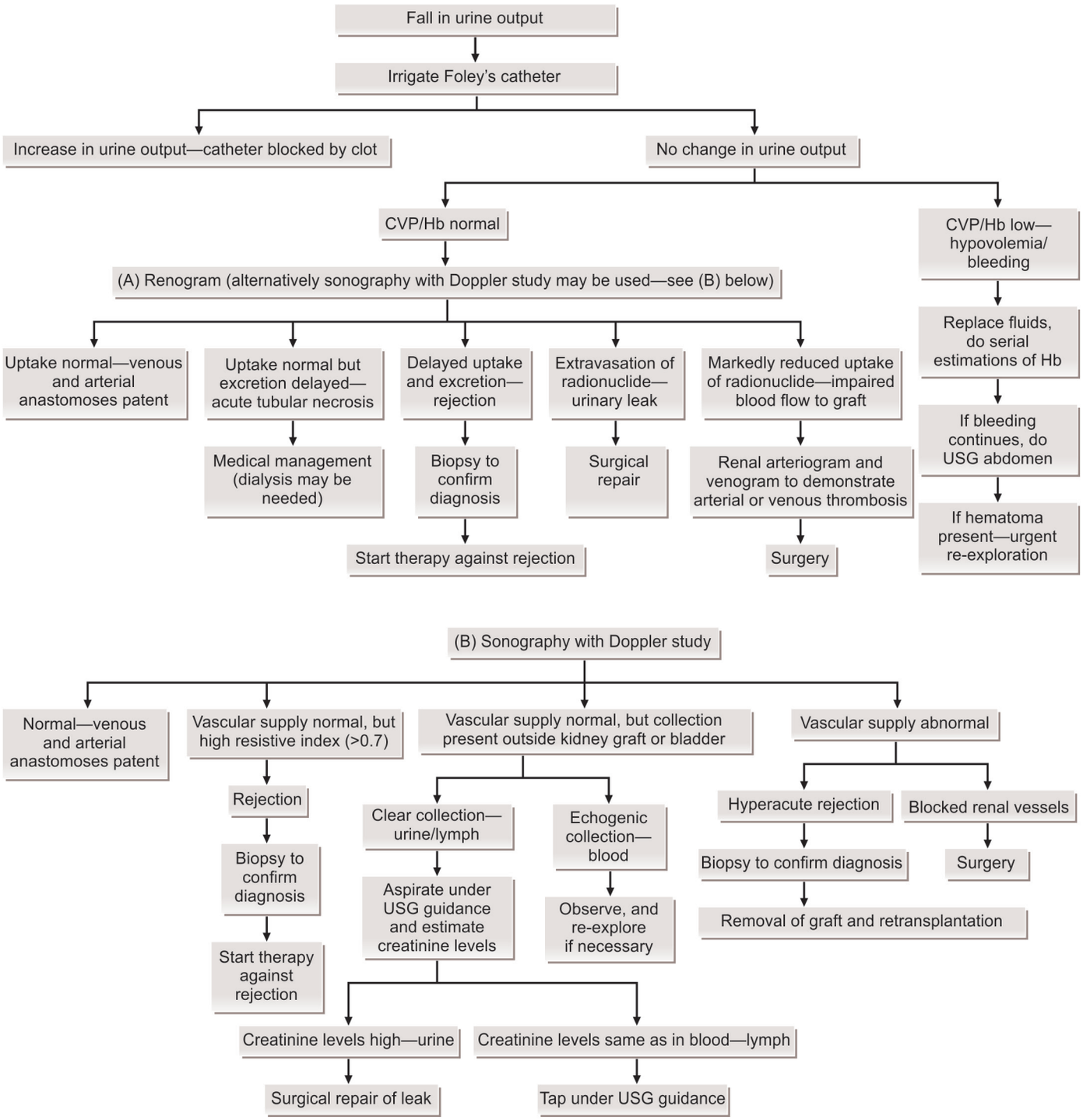
Treatment of acute rejection Treatment consists of the administration of a brief course of high dose corticosteroids [methyl prednisolone 500 mg intravenous (IV) everyday for 3 days). This is followed by the use of oral corticosteroids (0.5–1 mg/kg)] daily for several weeks, slowly tapered to a maintenance dose which is kept at a higher level compared to the preacute rejection period. In most cases, urine output improves, renal blood profile is rectified and serum creatinine is significantly reduced.

Occasionally some patients require a second course of IV steroids or a longer course of increased oral steroid therapy.

It is important to note that ganciclovir prophylaxis (5 mg/kg twice daily) tapered over 6 weeks must be given on initiating anti-rejection therapy for all patients with CMV-disparate DIR status.

Treatment of chronic rejection Chronic rejection is observed later in the natural history of a renal transplant in the 1–6 months period after transplant surgery or any time after 6 months. It is particularly observed in patients who have

Flowchart 1: Approach to postoperative oliguria in a patient with renal transplant: (A) using a renogram, and (B) using sonography with Doppler study


Fall in urine output
Irrigate Foley's catheter
Increase in urine output—catheter blocked by clot
No change in urine output
CVP/Hb normal
CVP/Hb low—hypovolemia/bleeding
(A) Renogram (alternatively sonography with Doppler study may be used—see (B) below)
Replace fluids, do serial estimations of Hb
Uptake normal—venous and arterial anastomoses patent
Uptake normal but excretion delayed—acute tubular necrosis
Delayed uptake and excretion—rejection
Extravasation of radionuclide—urinary leak
Markedly reduced uptake of radionuclide—impaired blood flow to graft
If bleeding continues, do USG abdomen
Medical management (dialysis may be needed)
Biopsy to confirm diagnosis
Surgical repair
Renal arteriogram and venogram to demonstrate arterial or venous thrombosis
If hematoma present—urgent re-exploration
Start therapy against rejection
Surgery
(B) Sonography with Doppler study
Normal—venous and arterial anastomoses patent
Vascular supply normal, but high resistive index (>0.7)
Vascular supply normal, but collection present outside kidney graft or bladder
Vascular supply abnormal
Rejection
Clear collection—urine/lymph
Echogenic collection—blood
Hyperacute rejection
Blocked renal vessels
Biopsy to confirm diagnosis
Aspirate under USG guidance and estimate creatinine levels
Observe, and re-explore if necessary
Biopsy to confirm diagnosis
Surgery
Start therapy against rejection
Removal of graft and retransplantation
Creatinine levels high—urine
Creatinine levels same as in blood—lymph
Surgical repair of leak
Tap under USG guidance

failed to respond adequately to treatment of acute rejection. It presents as a dysfunction of the transplant kidney, leading to progressive renal failure. Chronic rejection is outside the purview of critical care and is treated generally on an outpatient basis.

Unfortunately, there is no satisfactory treatment for chronic rejection of solid organ transplants including kidney transplants. Retransplantation is the only solution to this problem.

Infectious Complications[10]

Infections in the immediate postoperative period are bacterial and are similar to those observed following other major surgery. Wound infections, nosocomial pneumonia, urinary

sepsis related to urinary catheters or infections introduced through central lines are all observed. Gram-negative and staphylococcal infections are most frequently observed. When compared to other solid organ transplants, kidney transplant recipients have the lowest incidence of pneumonia; even so, pneumonia occurs in about 16% of patients and has a mortality of 10%.[4] In the first post-transplant month, the organisms responsible for pneumonia are Gram-negative bacteria (*Klebsiella*, *Escherichia coli, Pseudomonas*) and staphylococci. Though fungal infections (*Candida* and *Aspergillus*) are more often observed after the first month (between 1 month and 6 months), they may occur earlier in patients on a more intensive immunosuppressive regimen or in patients who have received prolonged antibiotic therapy. Bacterial pneumonias are sometimes caused by multidrug-resistant organisms, extended spectrum beta lactamases, methicillin-resistant *Staphylococcus* and vancomycin-resistant Enterococci.

The most common postrenal transplant infection is a urinary tract infection (UTI) with an incidence of 30% during the first 3 months after transplant surgery. UTIs can lead to pyelonephritis and bacteremic sepsis, generally caused by Gram-negative infections.

Most patients undergoing kidney transplants are on hemodialysis and have an indwelling catheter, arteriovenous fistula or arteriovenous graft, all of which could be the source of blood stream infection, generally due to Gram-negative infections.

Opportunistic infections generally occur between 1 month and 6 months of transplant surgery. In developing and poor countries where tuberculosis is endemic, tubercular infection is perhaps the most common and the most important infection to surface after transplant surgery. It can occur at any time frame after transplant surgery but is more often observed after the first month onward. The most frequent site is the lung and the most common mode of presentation is a pyrexia of unknown origin (PUO). A CT chest is mandatory as radiography of the chest may fail to detect the lesion.

Among opportunistic infections, the ones most commonly observed between 1 month and 6 months (after tuberculosis) are viral infections, fungal infections, nocardial infections and cryptococcal infections. *Pneumocystis jirovecii* is observed in the late post-transplant period and causes an interstitial pneumonia. Since the use of trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis, the incidence of *P. pneumonia* has declined significantly.

The most important viral infection generally occurring between 1 month and 6 months after transplant is CMV infection.[11] The two diagnostic tests in current use are—

- A polymerase chain reaction (PCR) quantitative assay.
- An antigenemia assay based on the identification of the late structural protein pp65.

The clinical features and management of CMV infections are discussed elsewhere.

Other viral opportunistic infections are those due to herpes simplex virus (HSV), varicella zoster virus (VZV) and the Epstein-Barr virus (EBV). EBV infections can present with mononucleosis like symptoms with fulminant widespread post-transplant lymphoproliferative disease—a form of B-cell lymphoma.

Fungal infections are generally due to *Candida* species and *Aspergillus* infections.[12] Oropharyngeal candidasis is the most common fungal infection. Systemic fungal infections (candidiasis, disseminated aspergillosis or *Aspergillus* infection of the lung) are particularly noted in patients on significant immunosuppression or on broad spectrum antibiotics. Systemic fungal infections with respect to their diagnosis and management have been described separately elsewhere.

Nonrenal Post-transplant Complications

Nonrenal post-transplant complications include complications in relation to the following—

Cardiovascular System

Left ventricular failure, congestive cardiac failure, ischemic heart disease, hypertension, hypotension and pericarditis have all been observed.

Respiratory System

Pulmonary edema and ARDS. ARDS is more likely in recipients with poor initial graft function and in those receiving antilymphocyte globulin for inducing immunosuppression. The mortality of ARDS in these groups of patients is well over 50%.

Metabolic Complications

These include fluid and electrolyte disturbances, notably hyperkalemia. Copious diuresis immediately post-transplant may result in hypokalemia. Hypomagnesemia and hypophosphatemia can also occasionally occur following copious diuresis seen immediately post-transplant. Hypomagnesemia is related to drug-related renal wasting (related to the use of cyclosporine, tacrolimus, diuretics and amphotericin B). Hypophosphatemia is secondary to loss of phosphates in the urine caused by secondary hyperparathyroidism; the use of glucocorticoids and antacids contributes to hypophosphatemia.

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CRITICAL CARE OF THE LIVER TRANSPLANT RECIPIENT

Liver transplantation is the standard treatment for patients with end-stage liver disease and acute liver failure. Currently, the survival rate after transplantation is 90–95% at 1 year and 70% at 5 years.[1]

Results in India today at the best centers in the country are as good as those reported from the United States.[2] In spite of these encouraging figures, liver transplantation carries with it a significant morbidity. The risk of developing complications and therefore the associated increase in morbidity and mortality is not just related to the inherent major surgical procedure that liver transplantation entails. It is related to the patient's preoperative state of health, the quality of the donor liver, initial graft function and peri- and postoperative anesthetic, and intensive care management.[3]

POSTOPERATIVE CIRCULATORY INSTABILITY[4]

Graft function depends not only on intrinsic recovery of hepatic cell function, but also on hemodynamic stability. Hypovolemia, pulmonary edema and deterioration in gas exchange within the lung can all adversely affect graft function and contribute to increased morbidity and mortality. Hypotension is commonly observed at or soon after surgery. Hypovolemia is an important cause. Acidosis, electrolyte disturbances, hypothermia, underlying ischemic heart disease may adversely affect cardiac function and further hemodynamic instability. Multiple blood transfusions may lead to citrate-induced hypocalcemia and could further depress circulation. Volume loss is often underestimated because of hemorrhage, sequestration of fluid into the third space and continuing formation of ascites. Subclinical pulmonary edema is frequently observed in the first 24 hours after transplantation. The quick relief of vasodilatation following transplantation increases the afterload of the heart and is an additional factor contributing to impaired cardiac function.

The potential cardiac and circulatory instability make it imperative that the postoperative condition is carefully monitored and that measures are taken to maintain or restore an adequate cardiac output, a stable circulatory system and well-preserved pulmonary function to ensure adequate blood supply and oxygenation to the graft.

Monitoring should involve an estimation of the preload and afterload of both right ventricle (RV), left ventricle(LV), cardiac output, central venous pressure (CVP), pressure in the pulmonary artery, intrathoracic blood volume (ITBV) and lung edema index (extravascular lung water). The application of the thermodilution single indicator (PiCCO) system is a monitoring system that allows the above as also other relevant hemodynamic parameters to be monitored.[5] Optimizing cardiac output will help to avoid excessive fluid administration and will prevent both pulmonary edema and congestion within the hepatic sinusoids. A persistent vasodilatory state after surgery may necessitate the use of a judicious combination of fluid plus inotropes and/or vasopressors. Failure to increase systemic vascular resistance or to reduce inotropic/vasopressor support is believed to indicate a poorly functioning graft.

POST-TRANSPLANT SURGICAL COMPLICATIONS

Postoperative Hemorrhage

Bleeding is common in the postoperative period and is due to several causes. Five percent of patients may require a re-exploration to control bleeding in spite of improved postoperative ICU care. Bleeding is from the large raw area left after removing the recipient liver, from collaterals secondary to portal hypertension, and to ongoing coagulopathy due to disturbances in coagulation, fibrinolytic and platelet function. The coagulopathy is further compounded by multiple blood transfusions that may have been necessary. Fresh frozen plasma (FFP), cryoprecipitate need to be given, as also platelet transfusions. Hyperfibrinolysis present during the operative period may continue postoperatively and may necessitate the use of aprotinin.

Vascular Complications

Vascular complications occur in 3–5% of patients.[3] Thrombosis is the most common early complication; stenosis, dissection and pseudoaneurysm formation are less frequent. The hepatic artery is most commonly involved, though any of the vessels involved in vascular anastomosis may be involved.

Hepatic artery thrombosis is the most common vascular complication, the reported incidence being 3–5% in adults and 5–8% in children.

Thrombosis of the hepatic artery in the very early post-operative period leads to acute hepatic necrosis. There is a marked rise in the liver enzymes, septic shock, encephalopathy and overall rapid deterioration. Doppler ultrasound confirms the diagnosis. Prompt exploration and anastomosis is done if the diagnosis is made early.[6] If hepatic necrosis is extensive, a retransplant is indicated.

Hepatic artery thrombosis may present in a less dramatic fashion. The donor bile duct receives its blood supply from the hepatic artery; bile duct ischemia results. The presentation is with a biliary leak, hepatic abscess, cholangitis, sepsis or an evolving biliary stricture. These patients ideally require a retransplant. Till such time as an organ is available, the bile duct needs to be stented.

Hepatic Artery Stenosis

Hepatic artery stenosis occurs in 10% of cases.[3] It can lead to biliary ischemia and hepatic dysfunction. Doppler ultrasonography usually establishes the diagnosis.

Portal Vein Thrombosis and Stenosis

Portal vein thrombosis (PVT) is less frequently observed, occurring in about 2% of patients. Clinical presentation varies. When PVT occurs early, it results in severe liver dysfunction. Ascites develops quickly and variceal bleeding results from raised portal and mesenteric venous pressures. A Doppler ultrasound can assess the patency. Patients with severe liver cell dysfunction need an emergent transplant.

Portal vein thrombosis can also be managed by thrombolysis, anticoagulation and stenting.[7] If PVT occurs late, liver function is usually preserved. Management is conservative with systemic anticoagulation.

Portal vein stenosis (PVS) is an uncommon complication. It should be suspected if there is an increased portal vein pressure on a Doppler ultrasound. PVS is treated by balloon dilatation of the vein or a surgical reanastomosis.

Hepatic Venous/Caval Complications

Hepatic venous thrombosis, stenosis (Budd-Chiari syndrome) is rare, with an incidence of 1% in deceased donor liver transplant and 1–10% in live donor transplant.[8] Presentation is usually with increasing ascites, graft dysfunction and occasionally edema and renal dysfunction. Doppler ultrasound usually demonstrates the hepatic vein thrombosis or stenosis; the findings can be confirmed by a venacavogram.

Balloon dilatation with or without stent placement is the treatment for hepatic vein/caval stenosis.[9] Anticoagulation is required if recurrence of the Budd-Chiari syndrome is to be prevented. Urgent retransplantation is warranted if hepatic venous blood flow is completely or almost completely obstructed.

Biliary Complications

Biliary complications occur in 10–15% of patients.[3] They are generally due to devascularization of the bile duct, technical faults during difficult biliary reconstruction and biliary leaks from the cut surface of a partial liver transplant.

Biliary Leaks

Biliary leaks generally occur within the first 10 days after transplant from the anastomotic site. The leak is due to dehiscence of the bile duct at the anastomotic site related to surgical dissection, which impairs blood supply around that site, or to hepatic artery thrombosis.

Less frequently biliary leaks may occur later than 3 months after transplantation and are usually due to persistence of earlier complications or a late hepatic artery thrombosis.

Anastomotic leaks can be successfully treated in most cases by endoscopic stenting if the leak is localized without major biliary spillage. An intra-abdominal bile collection (biloma) is managed by an ultrasonography (USG) or CT-guided drainage.

If the anastomosis is markedly disrupted or if there is a large biliary leak, surgical revision becomes necessary.

Biliary Strictures

Biliary strictures account for about 30% of biliary complications. They occur most commonly at the anastomotic site due to local ischemia or to technical error. Nonanastomotic strictures can also occur; diffuse intrahepatic narrowing of bile ducts is rare, but carries a worse prognosis. Biliary stricture results in a cholestatic jaundice. Cholangitis may be the presenting feature with fever, leukocytosis and right hypochondriac pain. Cholangitis in liver transplant patients may also be present in the absence of the systemic features described above. USG may be misleading as biliary duct dilatation may not be seen. Cholangiography is the diagnostic test which should always be performed to confirm the presence of a biliary stricture. The treatment of an anastomotic biliary stricture is by percutaneous or endoscopic balloon dilatation and placement of a stent across the stricture. The long-term success rate is close to 70%.

Nonanastomotic strictures resulting from hepatic artery thrombosis have a poorer prognosis. Dilatation of the stricture with stenting should be considered as a bridge to liver transplantation.

Treatment of diffuse intrahepatic strictures is unsatisfactory. Balloon dilatation and stenting of major strictures should be attempted as a palliative measure. Retransplantation is generally required.

Wound Complications

Wound complications are common in liver transplant patients. The most common wound complications are infection and hematoma formation. Direct wound contamination may occur from bile or bowel contents if a bilioenteric anastomosis has been done. Hematomas can form because of large collaterals in the abdominal wall and because of underlying coagulopathy.

Wound infections generally present toward the end of the first week. The infection may cause obvious symptoms and signs, such as fever, leukocytosis, erythema and a purulent discharge. At times, symptoms and signs may be minimal. Treatment of wound infections is the same as in non-transplant patients. Systemic antibiotics may be necessary in some patients.

POST-TRANSPLANT MEDICAL PROBLEMS

Medical problems after transplant fall into the following groups. Problems may arise: (1) due to side effects of immunosuppressive drugs used to prevent graft rejection; (2) due to the residual effects of liver failure which disappear when the graft starts to function well; (3) dysfunction of the transplanted liver and (4) other complications following surgery. These could involve almost any organ system within the body.

Primary Nonfunction of the Transplanted Graft

Technical complications like vascular and biliary complications described earlier can lead to a non-functioning or

poorly functioning graft. However, a dreaded complication after liver transplant surgery is a primary non-functioning (PNF) graft. PNF graft is defined as a syndrome that results from poor or no hepatic function from the time of surgery. It occurs in less than 5% of transplants and has 80% mortality.[10]

The etiology of PNF is not known. Donor risk factors that have been associated with PNF include advanced donor age, increased fat content of the donor liver, prolonged cold ischemia (>18 hours) and reduced size grafts.

The clinical features of PNF are an unstable, clinical condition after hepatic perfusion has been re-established. The patient is hemodynamically unstable, there is increasing acidosis, persistent coagulopathy, poor bile production and poor color of the liver graft. The patients remain unconscious in the ICU; liver cell function is markedly impaired judged by a prothrombin time greater than 20 seconds 4–6 hours after the transplant, increasing hypoglycemia, marked rise in serum transaminases (>5000 IU-L) and persistent coagulopathy. It is important to make an early diagnosis and distinguish PNF from hepatic artery thrombosis, acute or hyperacute rejection of the graft and infection.

The treatment of PNF graft is unsatisfactory. Recipients with a diagnosis of PNF should be on a continuous infusion of prostaglandin E 1 (PGE 1) starting with 0.005 mg/kg per minute increasing if well tolerated to a maximum of 0.03 mg/kg per minute. PGE 1 acts by dilating the splanchnic vascular bed thereby allowing better perfusion of the graft. The drug probably also has an immunomodulatory effect. Ultimately, the patients do far better with a retransplant. The latter should be done early before multiple organ failure develops.

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Rejection

Hyperacute rejection is uncommon, but the diagnosis should be entertained if graft failure occurs during the first post-transplant week. Acute rejection on the other hand is common after a liver transplant; 30% of patients suffer at least one bout of rejection after 1 week post-transplant. Clinical features of acute rejection are often mild fever, malaise, a rise in serum bilirubin and transaminases is generally observed. A mild asymptomatic disturbance of liver cell function may at times be the presenting feature. The diagnosis is proven by a percutaneous biopsy of the liver graft. Mild rejection is treated by increasing the dose of immunosuppressants. Moderately severe or severe rejection (as judged by histology) should receive IV methyl prednisolone 500 mg daily for 3 days followed by oral prednisolone 0.5–1 mg/kg to start with slowly reduced to a maintenance dose.

Small for Size Syndrome

The diagnosis of small for size syndrome (SFS) is based on hyperbilirubinemia and massive ascites during the early post-transplant phase without evidence of any technical problems.[11] The pathophysiology of the syndrome is hepatocyte damage secondary to portal hyperperfusion. Patients with SFS have a higher incidence of renal, pulmonary and septic complications.

COMPLICATIONS INVOLVING DIFFERENT ORGAN SYSTEMS

Neurological Complications

Decreased conscious level is very often due to the use of sedatives and narcotics. Metabolic encephalopathy due to fluid and electrolyte disturbances, renal insufficiency, and poorly functioning graft could also result in a decreased conscious level. Prolonged postoperative hypotension may result in hypoxic ischemic encephalopathy with obtundation and cognitive impairment.

Fluctuations in serum sodium levels can cause a central pontine myelinolysis; a diagnosis which can be proved by a magnetic resonance imaging (MRI) of the head.

Postoperative generalized seizures can complicate the course of the first 2 weeks of the postoperative period. Seizures could be due to metabolic problems, drugs, cerebrovascular accidents or infective pathologies in the brain (meningitis, encephalitis and brain abscess).

Neurotoxic side effects of calcineurin inhibitors include tremors, mental changes, focal neurological and visual disturbances. Posterior reversible encephalopathy syndrome (PRES) is an uncommon, but well-known complication of immunosuppressive therapy and solid organ transplantation.[12] The syndrome is due to reversible vasogenic edema chiefly involving the occipital cortex, but also involving other areas of the cerebrum. The diagnosis of PRES can be promptly made on an MRI of the head. The calcineurin-inhibitor drug should be stopped immediately.

Cardiovascular Complications

Most intraoperative cardiovascular (CVS) complications occur immediately after reperfusion of the liver. These include arrhythmias, ischemic changes, fluctuations in blood pressure and occasionally cardiac arrest.

The postreperfusion syndrome[13] is characterized by a decrease in the mean arterial blood pressure by at least 30% for 1 minute within the first 5 minutes. Rarely hypotension and bradycardia worsen, and may lead to cardiac arrest. Ventricular tachycardia and ventricular fibrillation have also been described in the early reperfusion phase.

A rare postoperative complication is acute right ventricular failure secondary to severe pulmonary hypertension.[14] The pulmonary hypertension in these patients must have been present prior to the transplant as an uncommon complication of portal hypertension. The underlying pathology in the pulmonary vasculature is a plexiform angiopathy.

Respiratory Complications

Pulmonary complications are invariably present. Early complications during the first week include pleural effusion,

pulmonary edema, atelectasis and ARDS. Complications due to infections predominate after the first week.

Hypoxemia should always be looked out for; all the conditions listed above could cause hypoxemia. Hypoxemia is also present in patients with the hepatopulmonary syndrome.[15] The syndrome is associated with portal hypertension, and is characterized by dyspnea, cyanosis, clubbing and orthorexia. The hepatopulmonary syndrome is reversed in the majority of cases after liver transplantation.

Renal Complications

Renal dysfunction is very common after a transplant. Ten percent have severe renal failure requiring dialysis. Renal failure whether pre- or post-transplant increases the mortality rate of transplant surgery.

Prerenal and renal causes account for most of the renal dysfunctions observed after surgery. Acute tubular necrosis may result from hypotension and prolonged ischemia. Post-transplant new-onset hepatorenal syndrome occurs as a primary manifestation of severe graft dysfunction and often indicates the need for an urgent retransplant.

Once renal dysfunction is diagnosed, diagnosis should be directed to the cause. Hypovolemia should be corrected, hypotension countered by inotropes or vasopressor after correcting the volume status. It is important to avoid nephrotoxic drugs. If renal function worsens, renal support may be necessary in the form of hemodialysis or continuous venovenous hemofiltration (CVVH). Indications for CVVH or hemodialysis include—

- Volume overload with pulmonary edema.
- Persistent worsening hyperkalemia.
- Persistent or worsening metabolic acidosis.

Infectious Complications

Infections[3,16] Incidence of infections is the highest after liver transplants when compared to other organ transplants. This is related to—

- The massive lengthy surgery.
- The poor condition of the recipient before the transplant.
- The potential for biliary and enteric contamination.

All attempts should be made to prevent infection. Prophylactic antibiotics against biliary tract pathogens are important. Other prophylactic drugs include trimethoprim-sulfamethoxazole against pneumocystis infection, acyclovir or ganciclovir against CMV and other herpes family viruses, and fluconazole/voriconazole against fungal infections. Scrupulous attention to central lines, arterial lines and aseptic suction of respiratory secretions through the endotracheal tube is of crucial importance.

As with all other organ transplants, infections during the first month after transplant are chiefly bacterial, but CMV infections may occur even during the first month. Bacterial infections usually involve the abdominal wall and the abdominal cavity. Wound infections, cholangitis, intra- or extra-hepatic abscesses and peritonitis are important intra-abdominal complications. Bacterial pathogens often originate either from the biliary tract or from the small bowel at the time of surgery, or later following a biliary leak or a biliary stenosis. Nosocomial pneumonia may occur particularly if the patient is on ventilator support for a long time.

From 2 to 6 months (at which time immunosuppression has been obtained through immunosuppressive drugs) after a liver transplant, opportunistic infections may necessitate admission to the ICU. Viral infections are frequent particularly CMV infection. Overall, this is the most common microorganism responsible for post-transplant infections. Though it classically appears after the first month, it may well be responsible for infection during the first month. The graft from a seropositive donor transplanted into a seronegative recipient, multiple blood transfusions and the use of anti-lymphocytic serum are risk factors for CMV infection. In the absence of prophylaxis, CMV infection occurs in 23–83% of patients though only 10–30% will develop disease. CMV infection is associated with increased incidence of graft loss and increased post-transplantation mortality.

Other viral infections between the second and sixth months include EBV, recurrence of HCV and adenovirus infections. Fungal infections are also observed. Infections due to *pneumocystis, candida, aspergillus* species and *Cryptococcus* should always be kept in mind.

Mycobacterial infections, either *Mycobacterium tuberculosis* or atypical mycobacteria, are important infections in developing poor countries where tuberculosis is highly endemic.

After the sixth month of surgery, ICU admissions are for acute infections common to non-transplanted patients. Infections in this period affect mainly the respiratory tract and are caused chiefly by the *Pneumococcus* and *Haemophilus influenzae.*

Management

It is important to identify the site of infection and the organism causing the infection. A low-grade fever may be the only manifestation of infection. A careful physical examination, laboratory tests, culture of blood and other body secretions and imaging studies generally allow a correct diagnosis. Treatment depends on the nature and site of infection. At times, particularly when dealing with serious infections, empiric therapy is necessary. Drug interactions between certain antibiotics chosen for treatment and immunosuppressive drugs should be kept in mind.

Gastrointestinal Complications

Gastrointestinal infections include—

- *Gastrointestinal bleed* Upper gastrointestinal (GI) bleeding can be due to several causes—stress, use of steroids, gastroesophageal varices and peptic ulcer disease. Bleeding from varices generally settles down

quickly; if persistent, a portal venous thrombosis is a strong possibility and needs investigation. Ulcerations of the GI tract may be due to infections, esophageal candidiasis and CMV infection.

Lower GI bleeding may be due to infective colitis caused by *Clostridium difficile* or CMV infection. These infections may also cause persistent diarrhea.

- *Ileus* is a common postoperative complication which settles down with time. Intra-abdominal infection is an important cause of ileus.
- *Bowel perforation* is a rare complication. Either the small or large bowel may be involved. Symptoms and signs are often not prominent, probably because of the use of corticosteroids and immunosuppressants. Early diagnosis and surgical repair is crucial. Even so, the mortality is high.

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CRITICAL CARE OF THE LUNG TRANSPLANT RECIPIENT

Lung transplantation (single, double lung and heart-lung) is now an established procedure in the West. Major technical complications following lung transplantation are therefore increasingly uncommon due to improvement in surgical techniques and peri- and postoperative management.

Complications following lung transplant surgery are considered under three heads—

- Early complications occurring 0–10 days after surgery.
- Complications in the intermediate postoperative period (10 days to 1 month).
- Late complications (1–6 months).

COMPLICATIONS IN THE IMMEDIATE POSTOPERATIVE PERIOD (0 TO 10 DAYS)

Technical Problems and Other Early Postoperative Complications—

- *Postoperative hemorrhage* severe enough to require re-exploration is indeed rare.
- *Pulmonary artery obstruction* due to anastomotic stenosis or external pressure. Pulmonary hypertension results and this may be the cause of hypoxia.
- *Left atrial anastomotic obstruction* because of faulty anastomotic technique can lead to pulmonary hypertension and unilateral pulmonary edema. CT pulmonary angiography should confirm this diagnosis. Re-exploration and correction of the anastomosis may be necessary.
- *Pleural complications* though not uncommon are of minor significance. These include: (1) pneumothorax which requires intercostal tube drainage. Pneumothorax arising from the lung graft is worrisome as it may denote airway dehiscence being responsible for a communication between the airway and the pleural space; (2) pleural effusions are common, particularly if there is a size disparity between the donor lung and the thorax. Pleural effusions are managed conservatively.
- *Airway complications* The most common airway complication is related to bronchial ischemia. This is because the donor bronchus has to rely entirely on collateral perfusion from the pulmonary circulation in the initial post-transplant period. The airway complications that ensue are partial or complete bronchial dehiscence, bronchial stenosis and bronchial infection. The clinical features of bronchial dehiscence are a persistent air leak observed in the early post-transplant period. Infection at the anastomotic site can lead to peribronchial inflammation, peribronchial abscess or fistula. Bronchoscopy is the preferred method of evaluating bronchial anastomosis. Appropriate antibiotics and/or antifungals should be used if there is evidence of infection corroborated by culture studies. Bronchial dehiscence or infection can lead later to bronchial stenosis. There is progressive increase in airway obstruction, both clinically and on lung function tests. Bronchial stenosis is relieved by balloon dilatation and stent placement. Cryotherapy has also been used; rarely surgical reconstruction becomes necessary.
- *Myocardial infarction* is generally due to pressure overload during the implantation procedure and can be prevented in most patients by promptly initiating cardiopulmonary bypass.
- *Atrial arrhythmias* are common; *ventricular arrhythmias* may also occur. They are managed in the usual fashion.

Complications due to Immunosuppression

Immunosuppression protocols by and large are the same for all solid organ transplants. The complications related to immunosuppression are also therefore similar. At times, the occurrence of dysfunction of the transplanted organ causes difficulty in the evaluation of complications produced by the immunosuppressive drugs. The early side effects of immunosuppressive drugs are renal and neurologic dysfunction due to cyclosporine, hyperglycemia, mental changes, and acute gastroduodenal erosions due to corticosteroids, and leukopenia, and thrombocytopenia from antilymphocyte preparations.

Infectious Complications

Infections in the immediate postoperative period are bacterial, and are similar in nature to those observed following other major surgery. Wound infection, nosocomial pneumonia, urinary sepsis related to urinary catheters, or infection introduced through central lines are all observed.

Bacterial infections are treated with appropriate antibiotics, and by removal of lines that may have triggered the infection. Many units in our part of the world use prophylactic antibiotics after transplant surgery. The danger of superinfection with resistant organisms must always be kept in mind following unnecessary and wrong use of powerful antibiotics.

Bacterial pneumonia is the most commonly acquired infection after lung transplantation and is generally due to Gram-negative infection. It can occur in the early postoperative period, as also at any time during the first 2 months. New pulmonary infiltrates either in the transplant lung or native lung require aggressive evaluation. Flexible bronchoscopic examination and culture of bronchoalveolar lavage (BAL) fluid, and if thought necessary culture of protected brushings are often necessary for diagnosis. Besides routine cultures, smear and culture for acid-fast bacilli (AFB) and fungal cultures should also be sent for.

Gastroesophageal reflux can be an important cause of recurrent aspiration pneumonia, particularly in chronic

Table 1: Degree of postgraft dysfunction

Grade	PaO_2/FiO_2	Radiological findings
1	>400	No
2	>300	Yes
3	200–300	Yes
4	<200	Yes

obstructive pulmonary disease (COPD) patients. Proton pump inhibitors, sucralfate and a propped up position are important for prevention.

Complications with Regard to Graft Function

Postgraft Dysfunction[1]

Postgraft dysfunction (PGD) is perhaps the most serious postoperative problem after lung transplant surgery. Some degree of PGD is observed in 80% of lung transplant patients; it is severe in 15% of patients.[2] This complication occurs hours to within 3 days after lung transplant (LT) and must be distinguished from infection and rejection which occur well after 24 hours. PGD can persist for hours to as long as 8 days after LT.

The syndrome of PGD[3] is characterized by a disturbance in gas exchange which may be sufficiently marked to cause well marked hypoxia. The radiological features include interstitial plus alveolar edema. There is a lowered pulmonary compliance and an increase in pulmonary vascular resistance. In severe cases, a radiographic examination of the chest shows a total or "white out" of the lung, the pathology of which is diffuse alveolar damage.

The degree of PGD can be graded on the basis of gas exchange abnormalities and radiological findings (Table 1).

Management[4]

- Patients who have marked gas exchange abnormalities with the radiological features of acute lung injury or ARDS need ventilator support with the usual lung protective strategies. Inhalation of nitric oxide is reported to decrease both hypoxia and pulmonary hypertension in these patients.
- Extracorporeal membrane oxygenation (ECMO), high frequency ventilation and differential lung ventilation have been used in very severe cases.
- Retransplant has been done on an emergency basis when conservative management has failed, but with very poor outcome.
- Instillation of bovine surfactant immediately after the establishment of the bronchial anastomosis has shown improved oxygenation, reduced incidence of PGD and enhanced post LT recovery.

Several risk factors may predispose to PGD. These include disruption of lymphatics, nerves, bronchial vasculature during surgery, lung injury during preservation or during lung surgery, use of cardiopulmonary bypass, prolonged ischemic time, and use of blood products.

Rejection of the Graft

There are three types of rejections: (1) hyperacute; (2) acute and (3) chronic.

Hyperacute rejection is rare, and if it occurs, does so in the early postoperative period. Hyperacute rejection is mediated by existing antibodies that attach themselves to the endothelium of the blood vessels within the donor lung. Activation of complement causes thrombosis of the vessels with quick rejection of the lung transplant graft.

Acute rejection Though acute rejection may occur in the early postoperative period, it generally does so 10–90 days after LT and is therefore considered later.

COMPLICATIONS IN THE INTERMEDIATE POSTOPERATIVE PERIOD (10 DAYS TO 1 MONTH)

Technical Complications

Though complications due to technical procedures or faults during surgery manifest in the immediate post-transplant period, they may occasionally do so after 10 days. These complications have already been listed earlier and do not require repetition. Complications with regard to various organ systems in the immediate postoperative period may also manifest in the intermediate postoperative period (10 days to 1 month).

Rejection

Acute Rejection

Acute rejection generally occurs from 10 days to 1 month after surgery. It may however occur up to as long as 90 days after lung transplantation. Fifty percent of patients, however, experience it within the first operative month. In fact rejection is the major complication in this period. It leads to graft dysfunction and it is vital to determine whether the dysfunction is related to rejection or to other causes such as infection.

The clinical features of acute rejection of a lung transplant are fever, malaise, cough and increasing breathlessness. The radiological abnormalities observed include a hilar flair, interstitial and/or alveolar shadows, generally diffuse, but occasionally localized, and the presence of a pleural effusion. The pleural fluid is an exudate with predominant lymphocytes. Acute rejection causes hypoxia with a lowered PaO_2 and deteriorating lung functions, characterized by a fall in the forced expiratory volume in the first second (FEV_1), and in the mid and late expiratory flow rates. A transbronchial biopsy shows characteristic perivascular and subendothelial mononuclear cellular infiltrates. A lymphocytic bronchitis or bronchiolitis is also observed. Transbronchial biopsy and a full study of the BAL fluid help to differentiate acute rejection from lung infection. The transbronchial biopsy is assessed according to the degree of perivascular infiltrate present and the degree of airway inflammation (Table 2).[5,6]

Table 2: Classification and grading of pulmonary allograph rejection

Acute rejection	
Grade A0	None
Grade A1	Minimal
Grade A2	Mild
Grade A3	Moderate
Grade A4	Severe
Airway inflammation-lymphocytic bronchitis/bronchiolitis	
B0	No airway inflammation
B1	Minimal airway inflammation
B3	Moderate airway inflammation
B4	Severe airway inflammation
BX	Ungradeable because of sampling problem; infection rate

Source: Yousem SA, Berry GJ, Cagle PT, et al. Revision of the 1990 working formulation for classification of pulmonary allograft rejection. Study group. J Heart Lung Transplant.1996;15:1-15.

A confirmed diagnosis of rejection is best made on histological grounds. In both heart and lung transplant, a histological diagnosis of rejection can be made at a point in time when clinical and other functional parameters are barely or only slightly altered. An early histological diagnosis of rejection can therefore lead to a suitable modification of immunosuppressive therapy and result in improved graft survivals. Surveillance transbronchial biopsy is recommended at 3 weeks, 6 weeks, 3 months, 6 months, 9 months and 12 months after surgery for both heart, lung and isolated lung transplant. This is because rejection can occur with minimal clinical symptoms or signs. Also clinical symptoms and signs and/or a fall in FEV_1 can be due to other causes besides rejection, as for example, following infection. Bronchoscopy, a BAL study and a transbronchial biopsy may therefore be necessary for other reasons as well.

Treatment of acute rejection Treatment consists of administration of a brief course of high dose corticosteroids (methyl prednisolone 500 mg IV daily for 3 days). In most patients lung function and radiographic improvement occurs in 48–72 hours. The intravenous (IV) therapy is followed by oral prednisolone (0.5–1 mg/kg per day) for several weeks, the dose being gradually tapered ultimately to prerejection levels. The dosage of immunosuppressants in use should also be suitably increased. Occasionally some patients require a second course of IV steroids therapy. If clinical features of rejection persist in an LT patient in spite of the above, a repeat bronchoscopy for BAL and a transbronchial biopsy is advised. In patients who have features of a persistent acute rejection, cytolytic therapy with OK T3 and antithymocytic globulin (ATG) should be considered.

It is important to note that ganciclovir prophylaxis (5 mg/kg twice daily tapered over 6 weeks) must be given on initiating antirejection therapy for all patients with CMV disparate D/R status.

Infection

Bacterial infection mentioned in the immediate postoperative period can continue up to 1–2 months after surgery. Bacterial pneumonia is an important complication after lung transplant.[7] It is generally due to Gram-negative bacteria and responds to antibiotic therapy. Depending on the microorganisms involved, aerosolized antibiotic therapy may also help.

Cytomegalovirus infection[7-9]can also occur during this period of time after a solid organ transplant. The incidence of CMV transplant is related to the serological status of both donor and recipient. Recipients who are negative for CMV and receive a CMV negative solid organ transplant should not develop CMV infection, provided they are not transfused with CMV positive blood products. Recipients positive for CMV who receive a CMV positive donor transplant generally rarely develop CMV infection because of their preoperative immunity. However, if a CMV positive recipient receives a solid organ transplant from a seronegative donor, reactivation of the recipient's CMV can cause CMV infection in the donor transplant. Again if a CMV negative recipient receives a transplant from a seropositive donor, reactivation of CMV in the donor transplant may well occur. In both the last two scenarios systemic CMV infection with a CMV viremia may result. In some of these immunosuppressed patients the serology for CMV may be negative though the PCR for CMV may be strongly positive.[9] Systemic CMV infection[7,8] is a potentially fatal infection characterized by fever, pneumonia, hepatitis, chorioretinitis and hemorrhagic colitis. The incidence of CMV infection in transplant patients has been significantly reduced by: (1) the prophylactic use of ganciclovir before, during and after transplant surgery; (2) the use of blood products which do not show the presence of CMV infection and (3) testing for CMV infection both in the recipient and donor through a serological test. Treatment of CMV infection has been dealt within a separate chapter.

Oral candidiasis[10] is not infrequently observed following the use of broad spectrum antibiotics and the use of immunosuppressants. Candidal esophagitis and fungal infections of the urinary tract are also observed. Topical antifungal agents can be used as prophylaxis against oral candidiasis. Fluconazole is of use in oral moniliasis and candidal esophagitis. It can, however, cause an elevation of cyclosporine levels, which need to be carefully monitored. There are a number of antifungal agents available for systemic use in patients with invasive candidiasis. Amphotericin B is the drug most frequently used in poor developing countries. It should, however, be noted that systemic fungal infections generally do not occur within the first month of transplant surgery unless induced by the prolonged use of broad spectrum antibiotics to treat bacterial infection, or the use of high dose steroids as a counter to acute rejection.

LATE COMPLICATIONS AFTER LUNG TRANSPLANT SURGERY (1 TO 6 MONTHS OF LUNG TRANSPLANT SURGERY)

A detailed discussion of late complications is outside the purview of this chapter as these do not generally merit critical care. However, acute rejection when it occurs late or chronic rejection may occasionally necessitate intensive care.

Technical Complications

Bronchial stenosis may manifest at this point in time and has already been discussed.

Rejection

As mentioned earlier, acute rejection occurs generally between 10 days and 1 month after surgery. It may appear later. *Chronic rejection* may be observed particularly in patients who have failed to respond adequately to treatment for acute rejection. Chronic rejection of the lung graft[11] is synonymous with bronchiolitis obliterans (BO).[12] This entity is characterized by cough, breathlessness and an otherwise unexplained fall in expiratory flow rates.[13]

Bronchiolitis obliterans, also called obliterative bronchiolitis is defined clinically by severe airways obstruction and histologically by obliteration of the terminal bronchioles.[11-13] It is the single leading cause of death more than 1 year after transplantation. It generally occurs 16–20 months after surgery, but has been reported to occur as early as 3 months after transplantation. Its incidence ranges between 35% and 50%.[11-13]

The most consistent risk factor is acute rejection, particularly acute rejection with an incomplete response to treatment, or recurrent acute rejection. Other risk factors include CMV infections, other community-acquired viral infections, gastroesophageal reflux disease, PGD, human leukocyte antigen (HLA) mismatches, older donor age and bronchiolitis obliterans (BO) with organizing pneumonia.[13]

Clinically BO may exhibit no clinical symptoms and is then diagnosed on lung function tests by the presence of airways obstruction, a lowered FEV_1 and reduced mid-expiratory flow rates. When it does produce symptoms, it generally manifests as an upper respiratory infection, with fever, cough and breathlessness, and is not uncommonly mistaken for one.[11,12]

An X-ray chest may not be of help, but CT chest may help in diagnosis. Air trapping during expiration in a high resolution computed tomography (HRCT) of the chest is a sensitive sign. HRCT of the chest may also show decreased peripheral vascular marking, tree in bud appearance, mosaicism and bronchial dilatation.[11,12]

Transbronchial biopsy is used both for diagnosis and to exclude other causes. The diagnosis is often not proven by a transbronchial biopsy. The International Society of Heart and Lung Transplantation (ISHLT) has established a staging system for BO.[12] This system is based on reduction in the FEV_1 of more than 20% from the baseline after transplantation and a fall in the FEF 25–75% with or without pathological changes observed on a transbronchial biopsy.[12]

Treatment of BO is high dose IV methyl prednisolone followed by tapering doses of oral corticosteroids. ATG, OKT, alemtuzumab, basiliximab are tried in patients who do not respond. *The purpose of treatment is to stabilize the rejection phase as long as possible.* Methotrexate, sirolimus, aerosolized cyclosporine, total lymphoid radiation and newer immunosuppressants have been tried with the above purpose in mind.

There is no permanent cure for chronic rejection. Retransplantation has been performed with comparatively poor outcome.

Complications due to Immunosuppresion

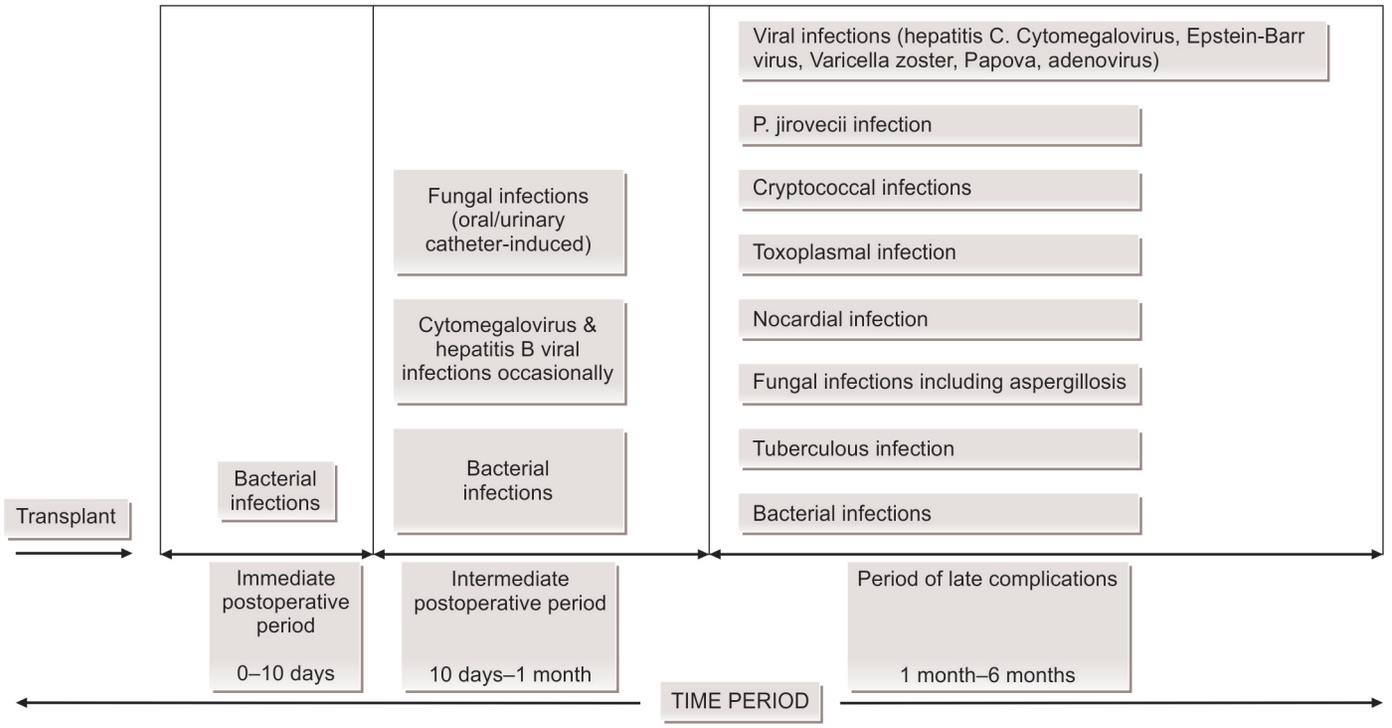
The chronic complications of immunosuppressive drugs during the late phase are cyclosporine nephrotoxicity, hypertension, lymphomas and skin cancer. The most common malignancy seen after lung transplant is B-cell lymphoid proliferation termed post-transplant lymphoproliferative disorder (PTLD) which appears to be related to EBV infection. When it occurs within one year of the transplant, the disease is localized and responds to a temporary reduction in immunosuppressants. If it occurs after a year of the transplant, if does not respond to reduction in immunosuppressants and needs cytotoxic therapy. The mortality for lymphoma in these patients is 70%.

Infection[14,15]

Tuberculosis and opportunistic infections predominate after 1 month of transplant surgery. In our part of the world, tuberculosis is the most frequently observed infection. It generally presents as a PUO and may be difficult to prove. Pleural effusion, lymphadenopathy within the chest or abdomen are most often due to tuberculosis. Investigations include a BAL study for AFB in patients with obscure lung shadows, and imaging studies to detect mediastinal hilar or intra-abdominal adenopathy. A therapeutic trial with antituberculosis drugs is at times necessary when all investigations have drawn a blank.

Important opportunistic organisms[14,15] causing infections in this phase are fungal infections (in particular, aspergillosis), *Nocardia, Pneumocystis carinii* infection, *Toxoplasma* and cryptococcal infections. Possible viral infections include CMV, HCV, EBV and papavoadenovirus.[7] Prophylaxis with trimethoprim-sulfamethoxazole is advised to prevent *P. carinii* infection. Flowchart 2 illustrates the time span for different infections following transplant surgery.

Flowchart 2: Time span for occurrence of common infections in the organ transplant recipient



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IMMUNOSUPPRESSION THERAPY IN ORGAN TRANSPLANTS[1-3]

Immunosuppressive drug regimes have been responsible for the great success of transplant surgery, and for the long-term survival of transplants. The critical care physician must be aware of the side effects of these drugs for two reasons—firstly they may be serious enough to necessitate critical care; secondly they need to be distinguished from other complications that follow transplant surgery.

The most important immunosuppressive drug in use today is cyclosporine. The drug is almost always used in combination with prednisolone. Some centers also add azathioprine to this immunosuppressive combination. A triple drug regime is often used in the hope that side effects from any one drug are lessened, and the combination may have an additive or even synergistic immunosuppressive effect.

IMMUNOSUPPRESSIVE DRUGS

Cyclosporine[4,5]

Cyclosporine is the chief immunosuppressant in use today. It prevents rejection, but is of little use in treating rejection once this has occurred. It is used intravenously in the immediate postoperative period, but, after gut function returns, the drug is given orally. IV administration carries a greater risk of nephrotoxicity than the oral use of the drug. The drug inhibits the production of intrarenal prostaglandins, and thereby induces renal vasoconstriction. The IV drug dosage can be profitably reduced by the use of antilymphocytic preparations in the early post-transplant period. This schedule prevents rejection, and will allow the kidneys to recover function after surgery.

Sandimmune is the original oil-based cyclosporine preparation. Almost all units use the newer microemulsified preparation, neoral. Sandimmune requires the presence of bile salts for absorption. Neoral is less dependent on bile salts for absorption. Absorption of cyclosporine from the gut may prove a problem after liver transplantation, as bile is diverted from the gut by a T-tube. The drained bile should be refed through the nasogastric tube, thereby allowing absorption of the orally administered drug.

Drugs such as phenobarbitone, warfarin, phenytoin, rifamycin, which increase the activity of the P450 system, lead to increased metabolism of cyclosporine, with inadequate blood levels of the drug. On the other hand, ketoconazole, fluconazole, and erythromycin lead to increased blood levels of the drug.

Cyclosporine levels should be ideally estimated in the blood either by immunoassay or by the high performance liquid chromatography method. The immunoassay method is generally adequate, though it overestimates blood levels of the drug in the presence of cholestasis and jaundice.

The most important side effect of cyclosporine is renal dysfunction. It can occur early in the post-transplant period, and needs to be distinguished from renal dysfunction due to rejection of the graft. A biopsy of the renal graft is generally necessary for this purpose. Other side effects include headache, seizures, myoclonus and hypertension. Gingival hyperplasia, hirsutism and hypercholesterolemia may also be observed. Hyperkalemia is an important side effect, and is related to hypoaldosteronism.

Tacrolimus [6]

Tacrolimus, like cyclosporine, is used to prevent acute rejection. It is protein bound, does not require bile salts for absorption and is given orally. Dose adjustments in patients with renal insufficiency are not necessary. As with cyclosporine, drug interactions between tacrolimus and other drugs can occur, thereby altering the blood level of tacrolimus. Side effects include hypertension, nephrotoxicity, tremors, abdominal pain and hyperglycemia.

Corticosteroids[1]

Corticosteroids are useful both for prevention and treatment of rejection. At surgery a large dose of methylprednisolone 15–20 mg/kg is given. This is progressively tapered to a maintenance dose of 0.1–0.2 mg/kg within 2 months.

The important immediate side effects of corticosteroids are hyperglycemia and mental changes severe enough to cause a psychosis. The hyperglycemia lessens once the steroid dose is reduced; it may however need a titrated dose of insulin for its control. The long-term side effects of corticosteroids are numerous—obesity, cushingoid features, hypertension, osteoporosis, peptic ulcer, premature cataracts and growth retardation in children.

Azathioprine[1]

This is useful in the prevention of rejection, but has no effect once rejection has occurred. Some units use azathioprine in their protocol from the outset; others use it after one episode of rejection has occurred. The major side effects are depression of the bone marrow and liver toxicity. The white blood cell (WBC) count is best kept more than 3,500/mm^3, and the liver functions should be monitored at periodic intervals.

Antilymphocytic Preparations[7,8]

These preparations are antibodies to lymphocytes, whose functions are thereby inhibited. They are used to both prevent and treat rejection. The two preparations available are: OKT3, a monoclonal preparation; and ATG, a polyclonal preparation.

In the immediate postoperative period, these drugs are given in sequential regimens with the purpose of delaying the initiation of cyclosporine therapy. Sequential therapy consists of an initial use of an antilymphocyte preparation, enabling renal function to improve and stabilize after surgery. Cyclosporine is added subsequently. The risk of renal dysfunction due to cyclosporine toxicity in the immediate postoperative period is thereby reduced.[9] This regime was initially used in kidney transplants, but its use has now been extended in some centers to include other solid organ transplants, where renal dysfunction is a possibility due to intraoperative insults, or to pre-existing renal disease. ATG is initially used in preference to OKT3. This is because OKT3 appears to be more effective in treating rejection, and can be given via a peripheral vein on an outpatient basis. The early use of OKT3 may lead to sensitization that may hinder the future efficacy of the drug in treating rejection, if and when rejection occurs.

Antilymphocytic preparations, besides preventing rejection, are used to treat rejection in patients who have not responded to prior steroid therapy. ATG and OKT3 are associated with significant side effects related to cytokine release from lymphocyte activation. These include fever, hypotension, bronchospasm and respiratory failure. The side effects can be controlled by the prior administration of methylprednisolone in a dose of 15–20 mg/kg. The antibodies in ATG can cross react with leukocytes (other than lymphocytes) and platelets, causing leucopenia and thrombocytopenia. A late hazard of antilymphocytic preparations is the development of lymphomas.

NEWER IMMUNOSUPPRESSIVE DRUGS

Several newer drugs are under trial and will probably come into use for post-transplant immunosuppressive therapy. One of the newer drugs in clinical use is sirolimus. Further experience should decide whether sirolimus should be used as a first line drug together with other immunosuppressants, or whether it should only be reserved for patients who are at high risk for renal dysfunction, or for those who have developed nephrotoxicity following the use of cyclosporine and tacrolimus. The drug is administered orally, and has a half-life of 60 hours. It is metabolized in the liver; dose adjustments need to be made in patients with hepatic dysfunction, but not in patients with renal dysfunction. Like cyclosporine and tacrolimus, sirolimus is metabolized by P450 enzyme systems. Drug interaction may occur with the use of drugs that interfere with this system. The main advantage is its comparative lack of nephrotoxicity. Side effects include hypercholesterolemia, hyperglyceridemia, anemia, leucopenia and thrombocytopenia have also been observed.[10]

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SECTION

22

Critical Care in Pregnancy

- Introduction
- Critical Illness Not Specific to Pregnancy
- Critical Illness Specific to Pregnancy

CHAPTER 74

Introduction

The critical care aspects of a pregnant patient have four differentiating features compared to the critical care of one who is not pregnant. First, there are specific differences in the physiology between the gravid and nongravid patients. The physician or the intensivist has to be aware of these changes if he is to distinguish the "normal" from the "abnormal". Secondly, critical care of the pregnant patient includes care not only of the woman but also of the fetus. Thirdly, diagnostic procedures, interventions and drug therapy that may be optimal for the patient may pose actual or potential hazards to the fetus. Finally, pregnant patients in critical care units could present with emergencies observed in non-pregnant women, and also with grave problems peculiar to the pregnant state.

This section first gives a very brief overview of the relevant physiological changes in pregnancy followed by relevant observations on critical illnesses in the obstetric patient not specific to pregnancy. It then goes on to describe the major critical illnesses requiring critical care that are specifically related to the pregnant state. These illnesses are—

- Preeclampsia-eclampsia and their variants—the hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome and the hemolytic uremic syndrome (HUS).
- The acute fatty liver of pregnancy.
- Amniotic fluid embolism.
- Septic abortion.

PHYSIOLOGICAL CHANGES IN PREGNANCY[1,2]

Physiological changes in pregnancy should be looked upon as an adaptive process which provides maximum support for the fetus and minimizes the stress on the mother. Support to the fetus consists of ensuring an adequate placental blood flow, thereby providing enough oxygen and nutrients to the fetus. Reduction in maternal stress is chiefly through an expanded maternal blood volume, which acts as a buffer to compensate for substantial blood loss that always accompanies even a normal delivery. This expanded blood volume is responsible both for an increased cardiac output and an increased flow through the placental vessels.[2]

CHANGES IN THE CARDIOVASCULAR SYSTEM

A rise in the diaphragm that accompanies advancing pregnancy causes the heart to be more horizontally placed so that the apex is shifted to the left. The cardiac silhouette often appears larger than normal on an X-ray of the chest.

Hemodynamic changes are characterized chiefly by an increase in cardiac output by 30–50%, most of which occurs by the first trimester. The increase in cardiac output is due to both an increase in stroke volume and cardiac rate. After about 6 months of pregnancy, the cardiac output may decrease by over 20% in the supine position because of pressure of the gravid uterus on the inferior vena cava; this results in a reduced venous return and a fall in cardiac output.

Peripheral vascular resistance and also pulmonary vascular resistance decrease during pregnancy. The hyperdynamic circulatory state in pregnancy is characterized by tachycardia, an increased cardiac output, and an increased pulse pressure with warm peripheries. There is a prominent third heart sound at the apex and a systolic flow murmur, which is generally best heard over the pulmonary area. There is also, to start with, a decrease in systemic blood pressure which reaches its nadir by the sixth month; the pressure then gradually increases, but

should not be greater than non-pregnant levels at any time during pregnancy.

Labor and delivery are associated with even greater stress. Cardiac output increases by over 40%; there is an additional 15% increase in cardiac output with each uterine contraction. Delivery of the fetus is associated with an even further increase in cardiac output, presumably because of autotransfusion of blood contained in the uterus. This extra cardiac stress can lead to decompensation in patients with background heart disease, or could induce a sharp rise in left atrial pressure, resulting in acute pulmonary edema in patients with mitral stenosis.

CHANGES IN THE RESPIRATORY SYSTEM

Several aspects of pulmonary function change during pregnancy. There is an increase in tidal volume by about 40% and a fall in residual volume by 20%, as also a fall in the expiratory reserve volume. The forced vital capacity is unaltered.

The total oxygen uptake is increased by 30–40 mL/minute and there is a disproportionate increase in minute ventilation by about 50% at full-term. This hyperventilation in pregnancy is probably hormonally mediated and results in a $PaCO_2$ <30 mm Hg.

In view of the increased oxygen consumption by pregnant women, the physiological changes in ventilation during pregnancy, and the fetal oxygen dissociation curve, higher parameters for oxygen are necessary in the presence of respiratory distress or failure. The goal should be to maintain an O_2 saturation above or equal to 95% to ensure adequate oxygenation to the fetus.

CHANGES IN RENAL PHYSIOLOGY

There is an increase in glomerular filtration rate, an increase in the creatinine clearance and lowered serum creatinine values (below 0.9 mg/dL). A serum creatinine of say 1.4 mg/dL which would be considered normal in a non-pregnant female would indicate significant renal impairment in a pregnant female. As pregnancy progresses, there is a reduced sensitivity to endogenous vasopressors; this is responsible for decrease in the systolic and diastolic arterial pressures and the widened pulse pressure.

CHANGES IN GASTROINTESTINAL PHYSIOLOGY

Most of the changes in the gastrointestinal tract are caused by progesterone-related alteration of smooth muscle relaxation. Decreased lower esophageal sphincter tone leads to gastroesophageal reflux. There is also a hormone-related generalized hypomotility of the GI tract.

The abdominal viscera are pushed laterally upward and posteriorly by the enlarging uterus. The displacement of viscera may lead to problems in the interpretation of physical signs associated with common inflammatory abdominal pathologies. Thus, as pregnancy advances, Mcburney's point and Murphy's sign do not have the same relevance as in non-pregnant patients.[3]

HEMATOLOGICAL CHANGES

These include an increase in plasma volume by 40–60%, and an increase in red blood cell mass by 25%. There is therefore often a dilutional anemia with an Hb concentration of 11 g/dL at 24 weeks of pregnancy. Biochemical changes include a fall in serum osmolarity and a slight decreased concentration in the serum levels of sodium, potassium, calcium and magnesium. The total proteins and serum albumin level are lowered in proportion to the degree of volume expansion. The levels of cholesterol and triglycerides may double in pregnancy.

The levels of clotting factors are altered. The fibrinogen level is as high as 600 mg/dL. Fibrin degradation products can be detected in traces. The risk of thromboembolism increases with a relative risk of 1.8 in gestation and 5.5 during puerperium. Increased venous stasis may contribute to the increased risk of thromboembolism.

IMMUNE SYSTEM

Pregnant women are at risk for certain infections. Reactivation of viral diseases and of tuberculosis appears more common in pregnancy. Varicella and pyelonephritis occurring in pregnancy are associated with more severe complications. The reason for this immune dysfunction has not been elucidated.

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CHAPTER 75

Critical Illness Not Specific to Pregnancy

INTRODUCTION

Serious illnesses necessitating critical care afflict pregnant and nonpregnant females equally. However, the pregnant state can at times influence the incidence, occurrence and clinical manifestations of both medical and surgical problems that require intensive care. The intensivist needs to focus attention not only on the pregnant patient but also on the unborn fetus. Emergencies characterized by hypoxia or fulminant infections increase fetal mortality and morbidity. Fetal monitoring in critical illness is therefore mandatory, particularly in conditions which affect maternal pulmonary or cardiovascular function. Auscultation of the fetal heart rate is an easy method to monitor the presence and degree of fetal distress. Continuous fetal heart monitoring by an electronic monitor is indicated in the viable or near viable fetus (beyond 23 weeks) during crisis situations or during surgical procedures when hypotension, anesthesia can lead to fetal compromise.

A very brief account of the possible influence of pregnancy on important critical illnesses[1] (not specific to pregnancy) is given below.

RESPIRATORY DISEASE[1,2]

The important causes of acute respiratory failure in pregnancy are acute severe asthma, pulmonary embolism, community-acquired pneumonia, aspiration pneumonia, pulmonary edema, and occasionally acute lung injury and acute respiratory distress syndrome (ARDS).

In our experience, acute severe asthma is the commonest medical emergency encountered in pregnancy. In asthmatic patients, pregnancy causes a worsening of the asthmatic state in about one-third of patients. The asthma remains unchanged in another third and may improve in the remaining third. Other than the influence of high dose corticosteroids on the fetus, there is no evidence that the use of beta-agonists or theophylline increases the morbidity or mortality of the fetus. Management of acute severe asthma in pregnant patients should be no different from that in the nonpregnant patients.

Pulmonary embolism is more frequent in the pregnant women as compared to the nonpregnant women, the risk factor being 1.8. This is because of hematological changes described earlier. The presentation most frequently observed is acute breathlessness. More often than not, there are no relevant physical findings and the patient is dismissed as "functional". Acute cardiorespiratory failure with hypotension and even shock is another presenting feature that is obviously promptly noticed. A computed tomography pulmonary angiography needs to be done and subcutaneous low molecular weight heparin in the usual dose should be promptly administered and continued through pregnancy. Warfarin is contraindicated in pregnancy because of the danger of an intracranial bleed in the fetus and because of its proven teratogenicity. Heparin should also be used for deep vein thrombosis even in the absence of pulmonary embolism. Patients with extensive deep vein thrombosis extending into the iliac veins or in patients who suffer from repeated pulmonary emboli, consideration should be given to the insertion of an inferior vena caval filter.

Community-acquired pneumonia is caused by the usual organisms, but treatment of pneumonia in the pregnant patient should include an awareness of the potential toxic effects of antibiotics on the fetus. Consideration should also be given to the harmful effects of diagnostic imaging involving the

use of X-rays. Hypoxia caused by severe pneumonia or acute severe asthma should be corrected adequately and promptly; close monitoring for fetal distress is mandatory. The arterial oxygen saturation should be kept more than 94–95% to avoid fetal compromise.

Aspiration as a cause of pneumonia is frequent in the pregnant patients because of the hormonally induced reduced tone of the lower esophageal sphincter and the increased transdiaphragmatic pressure due to the gravid uterus.

The causes of noncardiogenic pulmonary edema are the same as in the nonpregnant women. However, the use of tocolytic agents to retard the progression of labor is associated with an increased incidence of pulmonary edema. Also, pulmonary edema induced by tocolytic agents is observed to be at times more resistant to conventional therapy.[3,4]

Ventilator management of pregnant patients is no different from that of the nonpregnant patients. Attention should be directed to the avoidance of both high inflation pressures and of respiratory alkalosis. The objective is to prevent hypoxia in the mother and the fetus; yet a high maternal PaO_2 (>100 mm Hg) may lead to oxygen toxicity in the fetus. Higher than usual inflation pressure may, however, be necessary in late pregnancy to allow adequate minute ventilation. Management of ARDS in late pregnancy is distinctly more difficult than in the nonpregnant women.

CARDIOVASCULAR DISEASE[1,2]

The commonest cardiovascular disease in pregnancy necessitating intensive care is rheumatic heart disease with cardiac failure. Mitral stenosis is the most frequent cardiovascular problem meriting intensive care. Acute pulmonary edema in mitral stenosis is often related to the tachycardia and high output state which is the normal physiology of the pregnant patients. Pulmonary edema is worsened in the presence of atrial fibrillation with a fast ventricular rate. Digitalis and diuretics are safe during all stages of pregnancy.

Major cardiac surgery is best avoided during pregnancy unless absolutely necessary. The surgical procedure that may be lifesaving is a valvular commissurotomy for a tight mitral stenosis. However, coronary artery bypass surgery, valve replacement and repair of great vessels have all been performed at good centers with excellent results. Acute cardiomyopathy, though rare, is a recognized complication during the postpartum period. The cause is unknown and the treatment is as for any acute congestive cardiomyopathy.

RENAL DISEASE[1,2]

Pregnant patients are particularly prone to acute pyelonephritis. The latter may take a fulminant course, causing overwhelming sepsis, acute renal failure and multiple organ dysfunction syndrome.

The specific causes of acute renal failure related to pregnancy are dealt with later.

NEUROLOGICAL DISEASE[1,2]

Serious neurological problems are common to both pregnant and nonpregnant patients. However, cortical venous thrombosis with thrombosis of the intracranial venous sinuses is more frequent in the pregnant state and the puerperium. It often presents with seizures and is often wrongly diagnosed as epilepsy, or stoke or meningitis.

Myasthenia gravis may undergo remission or exacerbation during pregnancy. It may also be associated with transient neonatal myasthenia from transplacental passage of acetylcholine antibodies.

AUTOIMMUNE DISEASES[1,2]

Autoimmune diseases may remit or exacerbate during pregnancy. The two important autoimmune diseases which may need critical care during pregnancy are systemic lupus erythematosus and the antiphospholipid syndrome (APS). The latter syndrome is associated with an increased rate of abortion, fetal loss and maternal mortality.[4] Thrombocytopenia and the propensity to arterial and venous thrombi characterize this syndrome. Aspirin and the use of heparin are advocated in the management of APS presenting as an emergency meriting critical care.

ENDOCRINE DISEASE[1,2]

Control of insulin-dependent diabetes is more difficult in the pregnant state, yet ketoacidosis is uncommon. Gestational diabetes is characterized by reduced glucose tolerance initially diagnosed during pregnancy. Early gestational diabetes (before 20 weeks) often necessitates the use of insulin for proper control. There is also an increased risk of overt diabetes after pregnancy in these patients.

The features of thyrotoxicosis occurring in pregnancy may be wrongly attributed to the altered physiology in pregnancy. Tachycardia, palpitation and heat intolerance are common both to hyperthyroidism and to the pregnant state. Antithyroid drugs readily cross the placental barrier; they should be used with caution to prevent fetal hypothyroidism.

SURGICAL EMERGENCIES

Surgical emergencies occur with the same frequency as in the nonpregnant women and include in the main, acute appendicitis, acute cholecystitis, biliary colic, peptic ulcer disease, intestinal obstruction and inflammatory bowel disease.

Acute appendicitis is the most frequent surgical emergency requiring operative intervention. The risk of conservative management clearly outweighs the risk of surgery at all stages of pregnancy. Progressive enlargement of the uterus may displace the cecum upward, so that maximal tenderness may not be elicited over Mcburney's point. Ultrasound examination

is of great help in atypical presentations. Laparoscopic appendectomy is perhaps best confined to the first trimester; laparoscopic identification is difficult at full term.

Acute cholecystitis, particularly in the first and last trimester, is treated conservatively unless there are clinical features suggesting impending gangrene of the gall bladder. Surgical emergencies, like intestinal obstruction and volvulus, are difficult to diagnose particularly in advanced pregnancy. Surgery is indicated only after failure of medical management.

A surgical emergency that can be missed for a time is peritonitis due to accidental bowel perforation during the performance of a cesarean section. Abdominal guarding and rigidity are markedly reduced in these patients because of the stretching and laxity of the abdominal musculature caused by a fully gravid uterus. Persistent pain, free fluid within the abdomen and fever are warning signs that should not be ignored.

DRUGS USED DURING PREGNANCY

Drugs used for the mother can produce dangerous effects on the unborn fetus. The clinician must therefore be aware of the teratogenicity and toxic effects of drugs on the fetus. Though the mother's safety and life come first, the intensivist must consider possible alternative therapies which may be less dangerous to the fetus. Yet, the principle underlying the choice of a drug or therapeutic modality is that the anticipated advantage to maternal health and recovery far outweighs the theoretical risk to the fetus. Thus, the use of a lifesaving drug for which there is no good alternative is indicated in spite of its potential teratogenicity or toxicity to the fetus.

CARDIOPULMONARY RESUSCITATION IN THE PREGNANT WOMEN

If cardiac arrest occurs in a pregnant woman, resuscitative measures are exactly as routinely recommended.[5] Closed chest compression, defibrillation, use of adrenaline, vasopressors and other drugs should be carried out exactly as one would in a nonpregnant patient. It is often necessary to displace the uterus from the large abdominal vessels by a right hip wedge. If cardiopulmonary resuscitation is unsuccessful, the performance of perimortem cesarean section may be performed under appropriate circumstances, in the hope of extracting a live fetus.

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CHAPTER 76

Critical Illness Specific to Pregnancy

PREECLAMPSIA-ECLAMPSIA

GENERAL CONSIDERATIONS

Preeclampsia is an important and common complication of pregnancy. It generally becomes evident in the second half of pregnancy, during labor, or for the first time in the immediate puerperium, without there being preceding evidence of the disease. The disease is typically characterized by hypertension [blood pressure (BP) >140/90 mm Hg], significant albuminuria (≥300 mg/day) and generalized edema, which however may be more apparent on dependent areas, such as the feet. The disease always resolves over a period of time after delivery. The etiology of preeclampsia is obscure. The disease can be mild, moderate or severe, or graduate from mild to severe. The moderately severe and severe forms constitute a grave hazard to both mother and fetus, and necessitate critical care.

Eclampsia is characterized by generalized seizures (for which there is no other cause) in a woman with preeclampsia. However, eclampsia may strike suddenly in a pregnant woman who may often have no complaints or who exhibits mild to moderate hypertension very briefly before the onset of seizures.

It is best to consider preeclampsia–eclampsia as belonging to one clinicopathological spectrum extending from the milder forms of preeclampsia to the severe form of eclampsia.

INCIDENCE AND PREDISPOSING FACTORS

The incidence is probably about 1 in 20 or 30 pregnancies. It is more frequent in primigravidas than in multigravidas. Increasing maternal age, obesity, a history of previous preeclampsia and a family history of preeclampsia are also additional risk factors. Medical disorders that add to the risk of preeclampsia are pre-existing chronic hypertension, chronic renal disease, diabetes, antiphospholipid antibody syndrome, background connective tissue disease and severe migraine.

Placental/fetal factors contributing to an increased risk of preeclampsia include advanced gestational age, multiple pregnancy, poor placentation, hydatidiform mole, placental hydrops, trisomy 13 and triploidy (Box 1).

Box 1: Factors predisposing to preeclampsia

- Maternal factors—
  - Primigravida
  - Increased maternal age
  - Obesity
  - History of previous preeclampsia
  - Pre-existing hypertension
  - Chronic renal disease
  - Diabetes
  - Antiphospholipid antibody syndrome
  - Connective tissue disease
- Placental factors—
  - Advanced gestational age
  - Multiple pregnancy
  - Poor placentation
  - Hydatidiform mole
  - Placental hydrops
  - Trisomy 13
  - Triploidy

PATHOPHYSIOLOGY[1]

The pathophysiology remains obscure. The presence of the placenta is crucial to the development of preeclampsia. There appears to be a relative ischemia due to changes in the uteroplacental circulation. The changes are twofold. There is a partial lack of significant dilatation of the spiral arteries supplying the intervillous spaces; this dilatation is necessary to accommodate the expanded uteroplacental flow in the second half of pregnancy. There is also an obstruction of these spiral arteries by fibrin, platelets and lipid-laden macrophages. Whether this impoverished uteroplacental circulation due to changes in the spiral arteries are primary features or merely associated features of preeclampsia is not clear.

The pathology in the maternal circulation has excited a great deal of interest. The full picture of preeclampsia–eclampsia is not just a primary hypertension problem, but is the consequence of diffuse endothelial dysfunction which results in disturbed functioning of various organ systems, widespread changes in the walls and lumen of arteries and arterioles, and coagulation abnormalities. The current belief goes a step further in postulating that the endothelial dysfunction is merely one aspect of a generalized systemic inflammatory response that also involves leucocytes, clotting factors and other components of the inflammatory system. This systemic inflammatory response in a very mild asymptomatic form is believed to be present in the last trimester of normal pregnancy. Preeclampsia results when this pregnancy induced inflammatory response for any reason accelerates and leads to decompensation of one or more organ systems.[2] In other words, if this concept is indeed proven true, preeclampsia is merely an exaggeration or an aberration of a phenomenon present in every normal pregnancy.[2] It is the decompensation of various organ systems in severe preeclampsia that is responsible for complications that could easily lead to death.

CLINICAL FEATURES[2,3]

The minimum criteria for the diagnosis of preeclampsia are: (1) sustained BP elevation of 140 mm Hg systolic or 90 mm Hg diastolic in a previously normotensive woman after 20 weeks of pregnancy; (2) proteinuria of at least 300 mg in a 24-hour urine collection. Edema is frequent but is not included as an essential feature because some degree of pitting edema is often observed in the last trimester of a normal pregnancy. However, a sudden increase in body weight and edema often presages the occurrence of preeclampsia.

Hypertension is the essential feature and is caused by increased peripheral vascular resistance due to generalized endothelial dysfunction. The BP is typically unstable. The circadian rhythm is often altered, with initially a loss of the normal fall of BP at night, and later a paradoxical marked increase in BP during sleep.

Severe preeclampsia is associated with dysfunction of various organ systems.[3] It is of utmost importance to realize that changes in organ functions do not necessarily correspond with the degree of rise in BP.

Box 2: Organ system involvement in severe preeclampsia–eclampsia

- Maternal—
  - Central nervous system-cortical blindness, cerebral hemorrhage, grand mal seizures
  - Acute renal tubular necrosis
  - Acute cortical necrosis
  - Generalized edema, laryngeal edema
  - Acute left ventricular failure
  - Acute lung injury, acute respiratory distress syndrome
  - Disseminated intravascular coagulopathy
  - Hepatic infarction, intrahepatic hemorrhage and hepatic rupture
- Fetal—
  - Intrauterine death
  - Intrauterine asphyxia
  - Placental abruption

Generalized edema can occur but is inconsistent. Renal dysfunction could progress to acute tubular necrosis. Central nervous system (CNS) dysfunction takes the form of cortical blindness, cerebral hemorrhage and/or seizures (eclampsia). Involvement of the respiratory system can result in laryngeal edema and acute lung injury/acute respiratory distress syndrome (ARDS). Disturbances in the coagulation profile can lead to varying degree of disseminated intravascular coagulopathy (DIC). Hepatic dysfunction is characterized by right hypochondrial pain, tenderness, elevated liver enzymes, and rarely by hepatic infarction or even hepatic rupture. Left heart failure with pulmonary edema is also observed.

Fetal crises are frequently observed. They include fetal distress, fetal asphyxia, abruptio placenta and intrauterine fetal death.

Complications associated with severe preeclampsia–eclampsia are listed in Box 2.

Preeclampsia is best classified as mild to moderate or severe. Severe preeclampsia is characterized by at least one of the following additional criteria: (1) BP more than 160 mm Hg systolic or more than 110 mm Hg diastolic; (2) proteinuria more than 5 g in 24 hours; (3) serum creatinine more than 2 mg/dL; (4) noncardiogenic pulmonary edema (ARDS); (5) oliguria less than 500 mL/24 hours; (6) microangiopathic hemolytic anemia; (7) thrombocytopenia; (8) hepatocellular dysfunction; (9) symptoms of end-organ involvement (cortical blindness, severe headache, severe abdominal pain); (10) fetal growth restriction and (11) eclampsia (seizures in a pregnant woman for which there is no other cause).

ECLAMPSIA[2-4]

Eclampsia is merely the severe end of the spectrum of preeclampsia. The term is applied to grand mal seizures in

a patient with preeclampsia, in whom the seizures cannot be attributed to any other cause. As mentioned earlier, it can strike suddenly with the patient being unaware of having preeclampsia. Also the features of preeclampsia may antedate eclampsia by a very short period of time (less than a day or two). Seizures are often preceded by severe persistent headache. The occurrence of seizures is not necessarily related to the degree of hypertension, but is related to microangiopathic changes in cerebral vessels. Visual disturbances are frequent and often include cortical blindness. Cerebral edema, cerebral hemorrhage, DIC and ARDS are in our experience more often observed with eclampsia than in non-eclamptic patients.

There are two other syndromes which are currently considered complications or variants of the preeclampsia-eclampsia state. These are the syndromes characterized by hemolysis anemia, elevated liver enzymes and lowered platelets (HELLP syndrome) and the other characterized by hemolysis and uremia [the hemolytic uremic syndrome (HUS)].

HELLP SYNDROME[5]

There is still controversy as to whether this syndrome is a separate entity or falls within the spectrum of preeclampsia. The hemolytic anemia is due to a microangiopathic hemolytic process and rarely requires packed cell infusion. Thrombocytopenia is moderate and platelet counts less than 30,000/mm^3 are only rarely observed. The elevated liver enzymes that characterize the HELLP syndrome are due to hepatocellular injury, perhaps caused by vasospasm and microangiopathic changes involving vessels supplying the liver cells. The rise in hepatic serum enzymes may be associated with hepatic infarction, intrahepatic hemorrhage, subcapsular hemorrhage, and in rare instances hepatic rupture. The latter is an acute emergency needing prompt surgery. The maternal mortality in the HELLP syndrome is estimated to be 1–2%.

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HEMOLYTIC UREMIC SYNDROME

This syndrome is believed to be a variant of thrombotic thrombocytopenic purpura (TTP) without the presence of neurological features which typify TTP. It is rare in pregnancy and though considered to fall within the spectrum of preeclampsia may well be in our opinion, a separate rare entity. The HUS is characterized by renal dysfunction with high creatinine levels, an increase in the serum lactate dehydrogenase levels (>1000 U/L), and decreased haptoglobin levels. The direct Coombs test is negative. Coagulation studies are within normal limits.

Differential Diagnosis[3]

Hypertension occurring in the second half of pregnancy may be due to causes other than preeclampsia. These include chronic hypertension (pre-existing hypertension antedating pregnancy), gestational hypertension (pregnancy-induced hypertension with proteinuria), and elevated BP seen in pregnant patients with acute fatty liver. Acute glomerulonephritis or pyelonephritis complicating pregnancy can also cause hypertension.

Coagulation abnormalities can be caused by conditions other than preeclampsia. These include amniotic fluid embolism and acute fatty liver of pregnancy.

A combination of elevated liver enzymes and thrombocytopenia may occur with viral infections such as dengue, falciparum malaria and by other causes of hepatitis.

Management[1,2,6,7]

Severe preeclampsia merits critical care. The patient should be closely monitored with regard to vital signs and with regard to laboratory tests to evaluate functions of different organ systems. A central venous line is inserted before any serious disturbance in the coagulation profile occurs. A careful monitoring of the arterial BP is imperative. Arterial pH and blood gases are done and repeated as and when necessary. A close intake-output chart is vital and if possible the patient should be weighed daily.

Delivery

The definitive treatment of preeclampsia is delivery of the fetus. In severe preeclampsia, this should be undertaken promptly. The features of severe preeclampsia are then relieved and subside over a period of time. If, however, the mother's condition has stabilized and there is little or no organ dysfunction, conservative management with antihypertensives and support to all organ systems may be tentatively continued, only if the fetus is very immature. This is however controversial and should be entertained only when the anticipated benefit to the fetus is far greater than the risk to the mother or to both the mother and the fetus.

Control of Hypertension

The BP should be kept below 140/90 mm Hg. We use a combination of hydralazine, alpha-methyldopa and nifedipine to control BP. When systolic BP is more than 180 mm Hg or diastolic more than 110 mm Hg, hydralazine in a dose of 5–20 mg is given intravenously. An alternative is the use of labetalol, 20 mg intravenously given as a bolus. The drug is repeated, if necessary, at a higher dose of 30–40 mg every 15 minutes till a suitable fall in BP results.

Oral or sublingual nifedipine has been reported to produce a sharp fall in BP, but we have used this drug safely without any untoward effect. A carefully titrated and closely monitored infusion of nitroglycerine or sodium nitroprusside can also be used to control severe hypertension. Both drugs however cross the placental barrier and could exert toxic effects on the fetus.

It is debatable whether control of hypertension can reverse or delay maternal organ damage or increase fetal salvage rates. Hence, the dictum that prompts delivery is the treatment of choice in patients with severe preeclampsia.

Support to All Organ Systems

Oliguria (<30 mL urine/hour) can be due to a depleted intravascular volume, to cardiac failure or to isolated renal arteriolar spasm. Each of these requires appropriate treatment. Low-dose dopamine infusion at 2–4 µg/kg per minute may help to improve urine output, particularly in the presence of renal arteriolar spasm.

Pulmonary Edema

Pulmonary edema may be precipitated by volume overload, by left heart failure or by damage to the alveolar capillary membrane (acute lung injury). Hypoalbuminemia may contribute further to pulmonary edema. Diuretics, use of oxygen, use of digitalis for heart failure and ventilator support for acute lung injury become necessary.

All other organs deserve efficient support; cerebral edema is countered by the use of mannitol, and coagulation disorders by the proper replacement of coagulation factors. Patients with severe preeclampsia should be given seizure prophylaxis with intravenous magnesium (see below).

MANAGEMENT OF ECLAMPSIA[2,4,6,7]

Management consists of control of seizures, control of hypertension with drugs and prompt delivery.

Seizures are controlled best by administering a 4 g intravenous bolus of magnesium sulfate over 10 minutes, followed by a continuous infusion of 2 g/hour. The infusion rate is titrated so as to keep the serum magnesium level between 4.5 mg/dL and 8 mg/dL. If the patient has already been on intravenous magnesium as a prophylaxis (in severe preeclampsia), or if a recurrent seizure occurs after the initial seizure, a further 2 g bolus is administered.

Magnesium sulfate is undoubtedly the drug of choice for eclamptic seizures. If the latter are difficult to control in spite of the use of intravenous magnesium, a titrated infusion of diazepam (20–50 mg in 500 mL glucose) and intravenous dilantin sodium in an appropriate dose should be added to the therapy.

All organ functions need support, in particular the CNS, renal and hematological systems. Close monitoring of all vital parameters and of organ functions is imperative. Arterial pH and blood gases need to be frequently monitored; oxygen is almost always indicated. In patients with severe or recurrent seizures, or in obtunded patients, the airway should be promptly secured by endotracheal intubation. Mechanical ventilator support is indicated in the presence of hypoxia, recurrent or prolonged seizures, in the presence of pulmonary edema, and when the patient is heavily sedated to suppress seizure activity.

Nosocomial infections should be quickly diagnosed and treated with appropriate antibiotics.

MANAGEMENT OF HELLP SYNDROME[5]

The hemolytic anemia in this syndrome rarely needs packed cell infusions. Thrombocytopenia is generally not so marked as to require platelet infusions. Liver cell function should be supported by the use of intravenous glucose, vitamins and adequate nutrition. The latter may be difficult to achieve in the presence of right hypochondrial pain and vomiting. Symptomatic treatment for vomiting includes the use of phenergan, prochlorperazine and ondansetron.

Dexamethasone 10 mg intravenously 12 hourly usually results in clinical improvement and in a reversal of laboratory abnormalities. This therapy may permit some delay in delivery if the fetus is far too premature. Dexamethasone also promotes lung maturation in the fetus. The abnormalities however all return when dexamethasone is discontinued.

MANAGEMENT OF THE HEMOLYTIC UREMIC SYNDROME

The current treatment is the administration of plasma transfusions. Initially, 30–40 mL/kg of plasma is infused, followed by a reduction to 15–20 mL/kg once stabilization occurs. If improvement is not seen, plasmapheresis should be promptly used. Corticosteroids (100–200 mg hydrocortisone intravenously 8 hourly), dipyridamole, immunoglobulins, and immunosuppressants have all been tried with limited success. Platelet infusion should be avoided except perhaps when there is marked thrombocytopenia with severe bleeding, as platelets tend to promote further intravascular thrombosis.

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ACUTE FATTY LIVER OF PREGNANCY

GENERAL CONSIDERATIONS

This is a very rare but catastrophic complication of pregnancy. Its incidence is believed to be 1 in 10,000 to 1 in 20,000 deliveries. It is characterized by severe hepatic dysfunction with massive fatty infiltration within the hepatocytes occurring either during the last trimester of pregnancy or in the immediate postpartum period.[1] There are many who believe that this entity is a variant of preeclampsia, as the disease is frequently associated with hypertension and is more prone to occur in first pregnancies and with twin gestation.[2] Earlier, the mortality in acute fatty liver of pregnancy was reported to be over 70%. Currently, the mortality is close to 20–30% partly because less severe forms of the disease are recognized and partly because of early diagnosis and treatment.

The etiology of acute fatty liver in pregnancy is unknown. It is possible that the disease is more likely to occur in mothers who carry fetuses which have a genetic defect in the oxidation of fatty acids.[3]

CLINICAL FEATURES[1]

The clinical features are characterized by nausea, vomiting and increasing anorexia for 4–7 days. This is followed by jaundice and a tender enlarged liver. The serum bilirubin is raised to a varying extent; liver enzymes and alkaline phosphate are raised. Hypertension is frequently present and may be associated with albuminuria and edema.

In severe cases, there is progressive deterioration of liver cell function characterized by hypoalbuminuria, ascites, hepatic encephalopathy and a progressive worsening coagulopathy. Hypoglycemia due to worsening liver cell function, hepatorenal failure and metabolic acidosis are observed. Death, when it occurs, is due to severe multiple organ failure.

Pancreatitis is a noted complication and is associated with worsening abdominal pain and with elevation of serum amylase and lipase. Diabetes insipidus is a reported association; it may result in hypernatremia.

Improvement in the patient's condition generally occurs following delivery of the fetus. There is an increased incidence of fetal deaths from uteroplacental insufficiency, if delivery is delayed.

The *differential diagnosis* is from other causes of acute or fulminant hepatitis, in particular, viral hepatitis and drug-induced hepatitis. The diagnosis can be confirmed by a liver biopsy which demonstrates microvesicular fat within the hepatocytes. An ultrasonography of the abdomen demonstrates increased echogenicity of the liver due to a marked increase in fat content; a computed tomography (CT) or magnetic resonance imaging reveals decreased attenuation of the liver parenchyma.

MANAGEMENT

Critical care is required for patients with acute fatty degeneration of the liver.

Monitoring

Close monitoring of the patient and the fetus is imperative. Fetal heart sounds should be continuously monitored to detect fetal distress or compromise. Liver functions, blood chemistry, blood glucose and functions of all organ systems need careful monitoring, in particular, the renal and coagulation profiles. A central line should be inserted to help measure central venous pressure and guide fluid replacement early in the natural history of the disease.

Stabilization

Critically ill patients should be urgently stabilized. Hepatic encephalopathy should be treated on the usual lines (see Chapter Critical Care in Acute Hepatic Failure). Hypoglycemia poses a danger to both mother and fetus. Fluid and electrolyte disturbances are common and need to be restored to normal. Alteration of the coagulation profile should be countered by appropriate infusions of fresh frozen plasma, platelets and cryoprecipitate as indicated. Renal dysfunction is present in critically ill patients, necessitating fluid restriction and occasionally renal replacement therapy. Hypertension is frequently present and may require the use of hydralazine and other antihypertensives indicated earlier. If acute fatty degeneration of the liver is associated with other features of severe preeclampsia, magnesium sulfate should be used prophylactically (in the dose indicated earlier) to prevent seizures.

Delivery

Once the patient is stabilized, delivery is done preferably through a cesarean section. Spinal or epidural anesthesia should only be risked if the coagulation profile and platelets have returned to normal. General anesthesia is otherwise used, taking care to avoid agents which are hepatotoxic.

Following Delivery

Management involves meticulous multiorgan support, particularly to the liver. Proteins are avoided or sharply reduced in planning nutritional support. Calories should consist chiefly in the form of carbohydrates given as

intravenous glucose or through a nasogastric tube. Branched-chain aminoacids intravenously help to supply proteins (see Chapter Nutritional Support in the Critically Ill Adult). Lactulose 30 mL three or four times a day helps to reduce ammonia production and absorption from the large bowel. A bowel wash using metrogyl is also of help.

Fluid and electrolyte balance is important. Vitamin K should be administered daily and the coagulation profile kept normal through proper blood product replacement therapy. Nosocomial infection is frequent, particularly in ventilated patients; it needs the use of appropriate antibiotics.

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AMNIOTIC FLUID EMBOLISM

GENERAL CONSIDERATIONS

Pulmonary embolism is a dreaded complication during pregnancy, at labor or in the puerperium. The source of embolism is generally the deep veins of the lower limbs, occasionally the pelvic veins or the large uterine venous sinuses. Women particularly at risk are those confined to bed because of preeclampsia or eclampsia, or those who have had a cesarean section. Venous thromboembolism is considered an important cause of death in the above situations.

In contrast, amniotic fluid embolism is rare, but catastrophic. It was first described in 1926. The overall incidence is unknown, but is believed to be 1 in 8,000 to 1 in 80,000 deliveries.[1] The maternal mortality can be as high as 85%; the fetal mortality is less, about 20%. Although very rare, it remains the third leading cause of maternal deaths in the United Kingdom after thromboembolism and hypertensive disorders of pregnancy.[1]

This catastrophic emergency is associated with increased maternal age, multiparity, protracted difficult labor, placental disruption and signs of fetal distress as evinced by meconium-stained amniotic fluid. It has been reported as a complication of termination of pregnancy in the first or second trimester, during normal pregnancy and the puerperium. The greatest risk is during labor. The emergency is caused by the escape and release of amniotic fluid into the maternal pulmonary circulation, blocking the pulmonary vasculature and triggering an inflammatory host response mediated by leukotrienes and other arachidonic acid metabolites. Activation of the coagulation pathways leads to DIC.

CLINICAL FEATURES[2]

Massive amniotic fluid embolism is characterized by a sudden progressive deterioration in the clinical condition of the mother, characterized by hypotension, dyspnea, hypoxia, cyanosis, culminating in cardiac arrest.

If the patient survives the immediate catastrophe, the clinical features are those of ARDS. Hypoxia, tachypnea and crackles over both lungs with bilateral shadowing on the X-ray of the chest are observed. Tachycardia and hypotension are generally present.

A third presentation, generally associated with ARDS, is the occurrence of DIC probably triggered by the inflammatory response induced by the contents of amniotic fluid. DIC may occur in 40–50% of patients.

DIAGNOSIS

The diagnosis is suspected from the clinical presentation. There is no confirmatory diagnostic test during life. The classic autopsy finding is the presence of fetal squamous cells in the maternal pulmonary circulation.

MANAGEMENT

Treatment is supportive. It includes cardiopulmonary resuscitation, and circulatory support through volume infusions plus the use of inotropes and vasopressors. Intubation with mechanical ventilator support is mandatory. ARDS is managed on conventional lines as discussed in an earlier chapter (see Chapter Acute Lung Injury and Acute Respiratory Distress Syndrome). Coagulopathy should be treated with infusion of appropriate blood products. Prompt delivery of the fetus through a cesarean section should be considered if there is a cardiopulmonary arrest, which does not respond to resuscitative efforts.

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SEPSIS IN OBSTETRICS

GENERAL CONSIDERATIONS

Conditions leading to sepsis in nonpregnant females can also produce sepsis in pregnant females. Diagnosis is rendered difficult in the presence of a gravid uterus and by constraints on imaging techniques that could be potential hazards to the fetus. Management of sepsis unrelated to pregnancy and delivery is the same as in the nonpregnant females. Surgery is technically more difficult in the presence of a gravid uterus and surgical interference can pose a danger to the fetus.

The most important condition causing sepsis directly related to pregnancy is septic abortion; this section briefly deals with this entity.

Septic abortion is sepsis associated with the spontaneous or induced termination of a recent pregnancy. Septic abortion is much more frequent in poor, developing countries where abortion is often performed by quacks in filthy conditions and by crude and dangerous methods. The chances of complications are greater when abortions are attempted in later pregnancy and when dilatation of the cervix and evacuation procedures are performed.

Maternal sepsis can also occur after the delivery of a child at full-term, particularly if labor is conducted improperly with unsterile instruments. Maternal sepsis is also a feature of a dead, retained, macerated fetus within the uterus.

CLINICAL FEATURES[1,2]

In a patient with a recent history of instrumentation to end pregnancy, the cardinal features of sepsis are fever, lower abdominal and pelvic tenderness, tenderness of the uterus on vaginal examination and a serosanguinous or purulent vaginal discharge. Vaginal bleeding, sometimes exsanguinating, may at times be the presenting symptom.

Fever and tachycardia are invariably present. Tachypnea, hypotension and the features of increasing septic shock can evolve with frightening rapidity. Disturbances in organ function become manifest early. Elevated liver enzymes, a modest rise in serum creatinine and a slight prolongation of the prothrombin time are forerunners of multiple organ failure. In severe cases, DIC sets in with bleeding from various sites, in particular, from the uterus. Death occurs from hypotensive shock and/or multiple organ failure.

LABORATORY EXAMINATION

Blood, urine and cervical secretions should be sent for routine examination and culture. Leukocytosis is frequent, but severe leukopenia often accompanied by thrombocytopenia is also an indication of sepsis. Gram stain of cervical secretions may guide initial therapy before culture reports are available. This is of utmost importance in the early diagnosis of infection with *Clostridium perfringens* The latter appear as Gram-positive rods on Gram stain of cervical secretions or of curetted material. Imaging studies may reveal gas in the myometrium and in fulminant cases, a crepitus can be felt in the soft tissues of the vagina and vulva.

X-ray of the abdomen may also detect perforation of the uterus or bowel which may complicate the use of dangerous procedures to achieve abortion.

An ultrasound of the abdomen may reveal the presence of retained products of conception as also inflammatory pathologies and abscesses within the pelvis and in the adnexa. A CT of the abdomen and pelvis would help to define and localize an abscess even better than an ultrasound. It would also clearly reveal the presence of gas in the myometrium and soft tissues of the pelvis in clostridial infection.

Laboratory investigation should include determination of function of various organ systems; these parameters should be repeated as and when necessary. A coagulation profile is imperative as is the estimation of arterial pH and blood gases. An X-ray of the chest may reveal acute lung injury or even ARDS.

MANAGEMENT[1,2]

Principles of management have already been outlined in the Chapter Sepsis and Septic Shock.

Immediate intravenous use of appropriate antibiotics, which cover Gram-negative, Gram-positive organisms and also anaerobes, is mandatory. Antibiotic therapy may subsequently be tailored according to culture sensitivity reports. Clostridial infections are treated with 2 million units of penicillin G 4 hourly, intravenously. Hysterectomy may be lifesaving in serious clostridial infection.

All organ systems need support; the coagulation profile should be restored by infusion of appropriate blood products. Cardiorespiratory support is vital and seriously ill patients need to be intubated and kept on mechanical ventilation. Details of management have been discussed in the Chapter Sepsis and Septic Shock.

Pelvic surgery may be necessary to drain abscesses or collections of infected blood. Retained products of conception should be removed by careful curettage as they contribute to further infection. Close cooperation between the intensivist and the obstetrician is mandatory for patient survival.

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SECTION

23

The Critically Ill Child

- Cardiopulmonary Resuscitation in Infants and Children
- Respiratory and Hemodynamic Monitoring in Children
- Approach to Shock in the Pediatric Intensive Care Unit
- Hypertensive Emergencies in Pediatrics
- Heart Failure in Neonates and Children
- Acute Respiratory Failure in Children and Hyaline Membrane Disease
- Fluid and Electrolyte Disturbance in the Critically Ill Child
- Nutritional Support in the Pediatric Intensive Care Unit
- Pediatric Life-threatening Infections Requiring Critical Care
- Acute Kidney Injury in Infants and Children

compression by two hands like in adults. The ratio of chest compression to breathing is 5:1 at all ages.

In case of airway obstruction due to a foreign body, the child should be encouraged to cough. Relief of obstruction is attempted only if coughing is ineffective or respiratory difficulty worsens with increasing stridor. In children, the Heimlich maneuver consisting of subdiaphragmatic abdominal thrusts is tried, while in infants, back blows and chest thrusts are attempted, so as to avoid injury to abdominal organs. Following such maneuvers, rescue breathing is attempted, and if this is found to be unsuccessful, the procedure is repeated.

If breathing cannot be initiated and maintained by rescue breathing, bag and mask ventilation with oxygenation is necessary. Well-fitting masks of proper size, with a good seal around the nose and mouth are necessary. Smaller bags of 250–750 mL volume are used in children to deliver small tidal volumes. The pressure applied has to be just sufficient to inflate the chest. In neonates, two to three fingers are used to squeeze the bag, while in bigger children, the bag is squeezed by one hand. Gentle pressure is sufficient, and care should be taken to avoid a pneumothorax.

In most situations, basic life support is enough to resuscitate infants and children. In newborns, before initiating CPR, drying of the skin surface and providing optimal warmth, as also gentle tactile stimulation by rubbing the back or sole, are necessary to establish breathing. Suction of the nostrils and the oral cavity generally clears the airway. If breathing is not established, oxygen delivered by a catheter placed 1 cm from the nostrils is often adequate. In majority of cases, breathing is established by such maneuvers; if not, CPR is begun.

If breathing cannot be adequately maintained by bag and mask ventilation, endotracheal intubation (using an uncuffed tube) may become necessary. A laryngoscope with a straight blade is preferred in infants and small children. A proper-sized tube is selected as per the baby's size—this varies from 2.5 in premature babies to 3–3.5 in full-term neonates, and proportionately larger sizes subsequently. Tube size as depicted by the internal diameter (ID) may be approximated by the formula:

$$\text{ID (mm)} = \frac{16 + \text{Age in years}}{4}$$

Proper-sized suction catheters varying in size from French 5 upward are used. Various oxygen delivery systems may be used, including an oxygen hood. Oxygen is toxic especially in preterm neonates, and may lead to retrolental fibroplasia and bronchopulmonary dysplasia; hence, it should be used judiciously.

Vascular access is often difficult in infants and children. In newborns, the umbilical vein may be used for a short period, till a peripheral vein can be secured. In infants and children, intraosseous infusions of fluids may be tried in the tibial bone, and as soon as the circulatory state improves, a peripheral vein is secured. Emergency drugs may be administered through the endotracheal tube, though such an access may pose special problems. The amount infused through the endotracheal tube must be limited to 5 mL to prevent atelectasis due to altered or destroyed surfactant. Any drug that is administered through an endotracheal tube may form an intrapulmonary depot of the drug as it is not washed off quickly, and hence the drug may have a prolonged effect.

Fluids may have to be infused to maintain an adequate circulatory volume. A bolus of 20 mL/kg body weight of isotonic fluids like Ringer lactate or normal saline are administered as the first step in resuscitation of volume. Further infusions are decided by the circulatory status.

Certain medications may be required in the last step of CPR. As endotracheal intubation is often planned in children, premedication with atropine is ideal. A minimum dose of 0.1 mg of atropine is used at any age; the actual dose works out to be 0.02 mg/kg body weight. This is to avoid smaller doses which often cause a paradoxical central nervous system-mediated bradycardia. Other medications required are similar to those used in adults, and include sodium bicarbonate to counter acidosis, and inotropes for circulatory support. Thus dopamine, dobutamine, isoproterenol or epinephrine infusions may be necessary. The pediatric dosages of inotropes are as follows: dopamine infusion at 2–20 µg/kg per minute; dobutamine infusion at 5–20 µg/kg per minute; epinephrine 0.01 mg/kg (0.1 mL/kg of 1:10,000 solution) stat, followed by an infusion at the rate of 0.1–1 µg/kg per minute; isoproterenol infusion at 0.1–1 µg/kg per minute. Ventricular extrasystoles and rhythm disturbances are often due to hypoxia, and are thus abolished by oxygen administration. Lidocaine in the dose of 1 mg/kg stat, followed by an infusion at a rate of 20–50 µg/kg per minute may however be necessary. Fluid and electrolyte abnormalities are common in the pediatric age group, and the use of dextrose, dextrose saline and Ringer lactate infusions should be carefully monitored.

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CHAPTER 78

Respiratory and Hemodynamic Monitoring in Children

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INTRODUCTION

Serious illness in children often goes unrecognized. Since children have immature cardiorespiratory and renal compensatory mechanisms, children can deteriorate rapidly unless appropriate treatment is initiated promptly. It is therefore vital that clinicians caring for children are trained to identify serious illness in the early stages.

The principles of cardiorespiratory assessment in children are similar to those in adults. This chapter has highlighted only the important differences in the assessment and monitoring of children compared to adults. A full discussion on procedures, techniques of monitoring and calculation of various monitoring parameters is done in other chapters in the book.

CLINICAL ASSESSMENT

Identification of serious illness in a child is essentially clinical. The American Academy of Pediatrics has proposed a guideline, the *Pediatric Assessment Triangle (PAT)* to rapidly identify children in need of immediate supportive care.[1,2] The three observations in the PAT are *appearance, breathing* and *circulation*. The American Heart Association has proposed an approach in the pediatric advanced life support (PALS) guidelines[2] where the child is assessed in the format of *airway, breathing, circulation, disability* and *exposure.*

Appearance and Breathing

The assessment of airway and breathing is to evaluate oxygenation and is evaluated by assessing the respiratory rate and pattern.

Respiratory Rate

Vital signs are interpreted in the context of age-related norms for children. Table 1 illustrates the vital signs according to the age groups in children. Tachypnea is a basic sign of respiratory distress and a respiratory rate above 60 minutes is always abnormal. While assessing respiratory rate, it is important to note that respiratory pauses may occur in children less than 3 months of age and are usually less than 5 seconds. Pauses often occur in groups of three or more are separated by less than 20 seconds, and usually resolve by 6 months of age.[3]

Respiratory Pattern

Respiratory distress is often the first clue to an impending respiratory failure. Scoring systems, like the *Wood-Downes* score [4] (Table 2) and *Becker Pulmonary Index* score for asthma,[5] are often used to monitor patient progress. There are other scoring systems which include blood gases and pulse oximetry. It is however noteworthy that respiratory failure can occur without respiratory distress in central hypoventilation, and in metabolic disorders there may be tachypnea without respiratory disease.

The assessment of adequacy of breathing is given in Box 1.

Circulation

The assessment of circulation is done by a clinical assessment of peripheral perfusion and a record of blood pressure (BP).

Peripheral Perfusion

Capillary refill time (CRT) This is assessed by a firm pressure on the forehead, sternum or tibia and on the soles of feet in neonates.

Table 1: Normal vital signs according to age

Age	*Heart rate (beats/min)*	*Blood pressure (mm Hg)*	*Respiratory rate (breaths/min)*
Premature	120–170	55–75/35–45	40–70
0–3 months	100–150	65–85/45–55	35–55
3–6 months	90–120	70–90/50–65	30–45
6–12 months	80–120	80–100/55–65	25–40
1–3 years	70–110	90–105/55–70	20–30
3–6 years	65–110	95–110/60–75	20–25
6–12 years	60–95	100–120/60–75	14–22
12+ years	55–85	110–135/65–85	12–18

Source: Hartman ME, Chefetz IM. Nelson's Textbook of Pediatrics, 19th edition. 2011. pp. 279-96.

Table 2: Wood-Downes Score

Score	*Wheezing*	*Retraction*	*Respiratory rate*	*Heart rate*	*Ventilation*	*Cyanosis*
0	No	No	<30	<120	Good symmetrical	No
1	End expiratory	Sub/Intercostal	31–39	>120	Regular symmetrical	Yes
2	All expiration	Supraclavicular/nasal	40–60		Very reduced	
3	Inspiration and expiration	+ intercostal + suprasternal			Silent thorax	

Source: Wood DW, Downes JJ, Lecks H, et al. A clinical scoring system for the diagnosis of respiratory failure. Am J Dis Child. 1972:123(3):227-8.

Box 1: The assessment of adequacy of breathing

The work of breathing—
- Respiratory rate
- Recession
- Inspiratory and expiratory noises
- Grunting
- Accessory muscle use
- Flare of ala nasi

Effectiveness of breathing—
- Breath sounds
- Chest expansion
- Abdominal excursion

Effects of inadequate respiration—
- Heart rate
- Skin color
- Mental status

Normally the blanched area disappears in less than 3 seconds and more than 5 seconds is considered significantly abnormal. Despite its simplicity and utility, the CRT is not very specific or sensitive.[6]

Cardiovascular signs When peripheral perfusion is inadequate, the cardiovascular compensatory system gives rise to tachycardia, diminished pulse volume and decreased peripheral pulses compared to central pulses.

Core-peripheral temperature gradient This is a useful sign to detect hypoperfusion. The core temperature is recorded in the mouth, rectum or tympanic membrane and the peripheral temperature is recorded on the skin over the peripheries. A normal core-peripheral temperature gap is below 2°C, and a gap of more than 5°C implies marked hypoperfusion.

Systemic manifestations Hypoperfusion of brain and kidney can give rise to altered mental status and oliguria.

American College of Critical Care Medicine has defined shock in pediatric patients as tachycardia with peripheral signs, decreased peripheral perfusion, including decreased peripheral pulses compared to central pulses, CRT above 2 seconds, altered alertness, mottled extremities and decreased urine output. It is important to note that in pediatric patients, a fall in BP is not required to make a diagnosis of shock.[6]

Blood Pressure

Blood pressure is taken in the right upper limb, but in infants it is important to also check the BP in the legs to rule out the possibility of coarctation of the aorta. BP measurements are done by age appropriate cuffs standardized to the circumference of the arm as outlined in Table 3. The British Hypertension Society (BHS) recommends choosing from three cuff sizes: (1) 4 × 13 cm, (2) 8 × 18 cm and (3) 12 × 35 cm (adult cuff) and putting on the widest cuff that will fit the arm [National High Blood Pressure Education Program, American Heart Association (NHBPEP, AHA)].[7] The Korotkoff sound technique is recommended as the standard for children older than 1 year. In infants the best indirect measurement technique is an ultrasonic flow detector[6] since sounds are difficult to hear in infancy.

The lower limit of systolic BP should be below 60 mm Hg for neonates and below 70 mm Hg for 1 month to 1 year olds.

Table 3: Cuff sizes recommended by the American Heart Association

Cuff	*Arm circumference (cm)*	*Bladder width (cm)*	*Bladder length (cm)*
Newborn	<6	3	6
Infant	6–15	5	15
Child	16–21	8	21
Small adult	22–26	10	24
Adult	27–34	13	30
Large adult	35–44	16	38
Adult thigh	45–52	20	42

Box 2: The assessment of adequacy of circulation and perfusion

Cardiovascular status—
- Heart rate
- Pulse volume
- Capillary refill
- Blood pressure

Effects of circulatory inadequacy on other organs—
- Respiratory rate and character
- Skin appearance and temperature
- Mental status
- Urine output
- Mental status

Table 4: Categorization of hemorrhage and shock in pediatric trauma patients

System	*Compensated shock, mild hemorrhage, simple hypovolemia (<30% blood volume loss)*	*Decompensated shock, moderate hemorrhage, marked hypovolemia (30–45% blood volume loss)*	*Cardiopulmonary failure, severe hemorrhage, profound hypovolemia (>45% blood volume loss)*
Cardiovascular	Mild tachycardia Weak peripheral pulses Strong central pulses Low-normal blood pressure [SBP >70 mm Hg + (2 × age in years)] Mild acidosis	Moderate tachycardia Thready peripheral pulses Weak central pulses Frank hypotension [(SBP <70 mm Hg + (2 × age in years)] Moderate acidosis	Severe tachycardia Absent peripheral pulses Thready central pulses Profound hypotension (SBP <50 mm Hg) Severe acidosis
Respiratory	Mild tachypnea	Moderate tachypnea	Severe tachypnea
Neurologic	Irritable, confused	Agitated, lethargic	Obtunded, comatose
Integumentary	Cool extremities, mottling Poor capillary refill (>2 seconds)	Cool extremities, pallor Delayed capillary refill (>3 seconds)	Cold extremities, cyanosis Prolonged capillary refill (>5 seconds)
Excretory	Mild oliguria, increased specific gravity	Marked oliguria, increased blood urea nitrogen	Anuria

Abbreviation: SBP, systolic blood pressure.
Source: Adapted from Advanced Trauma Life Support Course. Chicago, American College of Surgeons.

For children between 2 and 10, the PALS recommends the fiftieth percentile for systolic BP as 90 + (2 × age in years) and the fifth percentile as 70 mm Hg + (2 × age in years). A BP below the fifth percentile is considered as hypotensive. A classification of pediatric shock is given in Table 4.

The assessment of adequacy of circulation and perfusion is given in Box 2.

DISABILITY

Disability is assessed by a neurological evaluation. A change in the level of consciousness is often a result of direct injury to the brain but can be a manifestation of cerebral hypoxia due to cardiorespiratory compromise. The alert/verbal/pain/unresponsive (AVPU) scale (Table 5) and the Glasgow Coma Scale (GCS) (Table 6) are used to assess neurological status. GCS is widely used method to evaluate neurological function. Patients with a GCS score below or equal to 8 require aggressive treatment including airway management and intubation.

Table 5: AVPU neurologic assessment

A	The child is awake, alert and interactive with parents and care providers
V	The child responds only if the parents or care providers call the child's name or speak loudly
P	The child responds only to painful stimuli, such as pinching the nail bed of a toe or finger
U	The child is unresponsive to all stimuli

EXPOSURE

This is the final step in the assessment of the child where the child is undressed and a full general and systemic examination is carried out, to look for coexisting illnesses, injuries and medical issues. In children, it is important to note that the general examination often gives much more important information than a systemic examination. An experienced clinician can identify a "sick" look in a child with a serious illness. This "look" has been described by the mnemonic *TICLS*.[1] The observations include: Tone, Interactiveness (playfulness), Consolability, Look (gaze) and Speech (cry). A child who is not seriously sick would have a good tone, respond to the mother and be comforted and playful. A sick child in contrast would be limp, irritable, and listless and have a weak cry.

Table 6: Glasgow Coma Scale

Eye opening	*Points*	*Motor response*	*Points*
Spontaneous	4	Obeys	6
To voice	3	Localizes pain	5
To pain	2	Withdraws	4
None	1	Flexion	3
		Extension	2
		None	1
Verbal response (older children)	Points	Verbal response (infants and young children)	Points
Oriented	5	Appropriate words; smiles, fixes and follows	5
Confused	4	Consolable crying	4
Inappropriate	3	Persistently irritable	3
Incomprehensible	2	Restless, agitated	2
None	1	None	1

Source: Adapted and modified from Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. Lancet. 1974;2:81-4.

MONITORING

Monitoring is essential to identify serious illness in a child, assess response to treatment, decide on the need for hospitalization and monitor during hospitalization. There is a gamut of devices for monitoring a critically ill child. The choice of device is dictated by the clinical assessment of the child, keeping in mind cost and availability of devices and available medical skills. Excessive dependence on technology is clinically confusing,[8] and there is no hard evidence that extensive monitoring improves clinical outcome.[9] Monitoring will be discussed under two heads: (1) assessment of gas exchange and (2) hemodynamic monitoring.

Assessment of Gas Exchange

Pulse Oximetry

Pulse oximetry is now referred to as the "fifth vital sign" in critical care assessment.[10] As a readily available noninvasive device to monitor oxygenation, the use of the pulse oximeter is now almost a part of clinical assessment. In general, most children have SaO_2 above 97%, but SaO_2 above 95% is considered reassuring. SaO_2 below 90% on room air suggests hypoxia and a red flag that these children need to be monitored carefully.

Pulse oximetry is used in any situation where hypoxia is suspected because clinical signs are not reliable in predicting hypoxia. In pediatric patients, a clinical assessment of hypoxia had a sensitivity of only 33% and the presence of respiratory distress had a sensitivity of only 74% in predicting hypoxia.[10] Patient management was changed 91% of times when SaO_2 was known. Pulse oximetry has therefore become an essential tool for assessing any child requiring cardiorespiratory monitoring.

Pulse oximetry is used to detect a hypoxic patient populations in a variety of clinical settings. It is routinely used to detect hypoxia during pediatric procedures, particularly when sedation is required, including dental care. The American Academy of Pediatrics recommends continuous pulse oximetry in patients receiving sedation and analgesia.[3,11] In the emergency room, reassuring saturations reduce the length of observations and permitted early discharges. It is also useful to assess the response to treatment as well as the need for hospitalizations.[12,13] In the ICU, continuous monitoring with the pulse oximeter is routinely advised. Pulse oximetry reduces the number of blood gases required in an ICU setting without compromising outcome.[13,14] Oximetry may be less prone to error and more accurate in the assessment of oxygenation in patients with cardiopulmonary disease when compared with arterial blood gas (ABG) measurement.[13] It is an important tool to assess the response to cardiopulmonary resuscitation in neonates and children.[1] Routine screening with pulse oximetry of newborns before discharge is an effective tool to identify newborns with congenital heart disease.[15] In pediatric patients where obtaining ABG is difficult or when blood gas facilities are not available, pulse oximetry is invaluable.

Pulse oximetry is also useful for hemodynamic monitoring.[3] Recording the BP in infants can be difficult. Pulse oximeters that display waveforms can be used to measure the systolic BP in infants. The disappearance of the waveform on inflation of the cuff as well as the reappearance of the waveform on deflation of the cuff may be used to record the systolic BP. Alternation in the waveform has also been found to correlate with pulsus paradoxus.

Pulse oximeters have several limitations and readings can be inaccurate due to motion artifacts, presence of COHb and MetHb and errors in transmitted light. Some of the newer oximeters overcome many of these errors. The development of reflectance oximeters, which do not rely on transmitted but on reflected light, are under way. Other technologies are being developed[12,14] to assess tissue oxygenation and brain oxygenation and perfusion.

Pulse oximetry remains the most commonly used monitoring device in children. A clinician aware of its limitations can use it effectively to monitor children noninvasively with reasonable accuracy.

Arterial blood gas It is the traditional method for assessing oxygenation (PaO_2), ventilation ($PaCO_2$) and acid-base status (HCO_3, pH) and remains the gold standard for assessing respiratory status in a critically ill child. It is used intermittently to confirm blood gas status in a child being monitored noninvasively through pulse oximetry. Arterial cannulation is preferred when one anticipates the need for frequent blood gas sampling and when continuous BP monitoring is required in a critically ill child. Arterial blood sampling is sometimes necessary when venous blood sampling is difficult due to vascular collapse.

An ABG analysis is the best indicator of the physiological status of the cardiorespiratory system. The PaO_2, $PaCO_2$ and the pH/HCO_3 give the best indicator of the oxygenation, ventilation and the acid-base status in the critically ill patient. The blood gases can be assessed by the arterial or venous blood gases and transcutaneous blood analysis. Values of arterial PaO_2 below 85 mm Hg are usually abnormal for a child breathing room air at sea level. Values of arterial $PaCO_2$ above 45 mm Hg usually indicate hypoventilation, severe lung disease or a compensatory response to metabolic alkalosis.

Venous blood gas Venous blood gas (VBG) sampling is performed when arterial sampling is difficult since central venous access is usually available in a critical care setting. A VBG can be performed using a peripheral venous sample (obtained by venipuncture), central venous sample (obtained from a central venous catheter), or mixed venous sample (obtained from a pulmonary artery catheter). A VBG measures the venous oxygen tension (PvO_2), carbon dioxide tension ($PvCO_2$), acidity (pH), oxyhemoglobin saturation ($S\dot{v}O_2$), and serum bicarbonate (HCO_3) concentration. $PvCO_2$ and venous pH are used to assess ventilation and acid-base status, but measurement of PvO_2 is unreliable. A VBG is therefore often used in conjunction with pulse oximetry. Venous blood gases from a central vein or pulmonary artery ($S\dot{v}O_2$) are used to guide resuscitation during septic shock.

Transcutanous blood gas determination This involves measurement of PO_2 and PCO_2 by monitors placed on the skin electrochemically. Electrodes are attached to the skin on non-bony well-perfused areas like the abdomen, inner thigh and chest.[11] The monitors have a heating element which warms the skin up to 42–44°C and therefore arterializes the underlying skin. It is therefore reliable only when the BP and perfusion are normal. It is noninvasive, permits continuous monitoring of blood gases and reduces the need for frequent blood gases. The main advantage is in neonates where its readings are accurate over a wide range of PaO_2 values.[15,17] The disadvantage is that the instrument needs frequent calibrations and frequent site change to avoid skin burns[16,17] and an overestimated PaO_2 in the hypoxic range. Due to these limitations, these monitors are rarely used in the pediatric intensive care unit (PICU).

Capnography Capnography is the noninvasive measurement of CO_2 in the exhaled breath ($ETCO_2$). Capnogram refers to the graphic representation of CO_2 as a waveform over a period of time. CO_2 monitors can be either mainstream or sidestream.[13,17] Mainstream monitors are attached to the endotracheal tube and are generally used in ventilated patients. Sidestream monitors detect CO_2 from a nasal or oral cannula and can be used in the ventilated or in spontaneously breathing patients. In sidestream monitors, high flows and increased dead space make monitors less reliable in children. This problem has now been overcome by low flow microstream capnometers which require a minimal sample flow rate (50 mL/minute) enabling its use even in neonates and infants.

The normal $ETCO_2$ value is usually 2–5 mm Hg less than the $PaCO_2$.[14] The correlation between arterial $PaCO_2$ and $ETCO_2$ is reliable when the lungs are normal, and the problem is with ventilation or perfusion. In patients with pulmonary disease or mixed ventilation and perfusion illnesses or metabolic derangements, results are difficult to interpret, and $ETCO_2$ is useful only to document trends over a period of time.

The use of capnography in children is similar to its use in adults.[14,18] In intubated patients, capnography is of greatest value for emergency departments and emergency medical services for confirming placement of endotracheal tubes, continuous monitoring of tube position during transport, assessing the status of patients in cardiac arrest, and monitoring the respiratory status of patients undergoing procedural sedation. In spontaneously breathing patients, capnography can be helpful in monitoring the status of patients with seizures, acute respiratory distress, unconsciousness and metabolic acidosis.

Hemodynamic Monitoring

Electrocardiography

Heart rate is the most common parameter monitored in the PICU. Children increase cardiac output more by increasing the heart rate than increasing the cardiac contractility, and an increase in heart rate is an important sign of circulatory insufficiency. Trends in heart rate can often guide fluid requirements and choice of inotropes. ECG can also assist in detecting rhythm disturbances, hyperkalemia or ischemia.

Noninvasive Blood Pressure Measurement

Automated BP devices which measure BP noninvasively through the oscillometric method are now routinely used in PICUs.[14] These devices have reduced the errors associated with manual methods. Using the correct cuff size improves accuracy.[7,14] A narrow cuff produces a high pressure and a wide cuff produces a low pressure. The American Heart Association recommends that the width of the inflatable bladder be 40% of the mid arm circumference of the limb and the length should be twice the width. Slow deflation further improves accuracy. Noninvasive BP devices are widely used in PICUs since inserting and maintaining arterial cannulas in young children is often difficult. One should however be aware that the accuracy of noninvasive monitors is reduced in the presence of hypotension, dysrhythmias and limb edema. The readings are falsely elevated in hypotension and reduced in hypertension. It is therefore recommended to monitor BP continuously through invasive arterial cannulation in the critically ill child.

Arterial Blood Pressure Monitoring

Children admitted to an ICU need an accurate assessment of circulatory status. Clinical signs of circulatory insufficiency are seen long before a fall in BP and indicate the need for accurate BP monitoring. Due to technical difficulties in arterial cannulation, noninvasive BP monitoring is frequently

practiced in the PICU. It should be emphasized however that direct BP readings are 5–20 mm Hg higher than indirect measurements[19] and intra-arterial recordings are considered the standard of care for monitoring BP in a critically ill child.

The technique, monitoring and complications of arterial cannulation are the same as in adults.[20] The radial artery is the most commonly used site in children. In newborns, the umbilical arteries are used in the first week of life. In infants with patent ductus arteriosus, the right radial artery represents the preductal oxygenation and the left radial represents postductal values. Other sites used for cannulation include: ulnar, axillary, femoral, dorsalis pedis and posterior tibial.

Central Venous Pressure Monitoring

Indications for central venous access include insertion of central venous catheters for administration of medications or fluid, parenteral nutrition, hemodynamic monitoring, plasmapheresis or hemodialysis. Central venous access may be necessary in patients with poor peripheral venous access.[21]

Central venous pressure (CVP) monitoring is used to guide fluid therapy in patients with shock, myocardial impairment or severe pulmonary disease. In adults, the flow directed balloon tipped pulmonary artery catheter has somewhat replaced central venous pressure monitoring because it is more reliable in patients with pre-existing cardiac and pulmonary disease.[20] In children, however, CVP monitoring continues to have a role to guide fluid therapy. In the specific setting of septic shock, CVP monitoring is an important component of "goal directed therapy". Measurement of central venous oxygen saturation is a part of the treatment of septic shock.

The normal CVP is 1–5 mm Hg. A CVP greater than 7–10 mm Hg is considered high. The determinants of CVP are ventricular function, intravascular volume and pulmonary vascular resistance.[20,22] A low CVP indicates low return of blood to the right atrium and indicates the need for more fluids. Low CVP is also seen in sepsis and spinal cord injury due to reduced vasomotor tone. Unlike adults, children usually have good cardiac reserve and tolerate fluid challenges well. Pediatric intensivists resort to CVP monitoring only if adequate fluid challenges do not restore BP. A high CVP indicates that there is cardiac dysfunction and the heart is unable to pump the blood or that there is fluid overload.

Left Atrial Pressure Monitoring

The CVP offers effective guidelines for fluid therapy only when the myocardial contractility and lung functions are normal. In critically ill children, particularly after cardiac surgery, the CVP is a poor predictor of LV end-diastolic pressure, and these children need a surgically placed left atrial catheter. These lines are used infrequently in children and are usually removed within 2 days to reduce complications.[20]

Cardiac Output

Cardiac output is the volume of blood ejected by the heart each minute, measured in liter/minute. Assessment of cardiac output can be done indirectly or directly. Direct assessment of cardiac output can be done noninvasively by echocardiography or by invasively by cardiac catheterization. Cardiac output is determined by the following factors: heart rate, preload, cardiac contractility and afterload.[20] Indirect assessment of cardiac output involves assessing each of these factors. An accurate evaluation of the physiologic status of the circulatory system helps in the choice of medications to support cardiovascular insufficiency.

Invasive cardiac output monitoring is usually needed only in cardiac cases. Cardiac output can be measured by different techniques including thermodilution, CO_2 rebreathing and dye dilution. The common variables calculated include cardiac index, stroke index, pulmonary and systemic vascular resistance, stroke work index and oxygen delivery. A detailed discussion on these values is beyond the scope of this chapter.

Noninvasive assessment of cardiac function is routinely done at the bedside by echocardiography.[14,23] Cardiac contractility is assessed by the SF (Shortening Fraction) and the EF (Ejection Fraction). The SF or the percent change in ventricular diameter gives a measure of the global systolic function. The normal SF values are 29–41%. The EF uses the percent change in end diastolic volume to assess cardiac contractility. The normal EF value in children is 60% ± 7%. The echocardiography also gives an estimate of the diastolic function and afterload.

Assessment of Intravascular Volume

Optimum fluid therapy is crucial in intensive care, particularly in children. Half the patients will improve their cardiac output and oxygen delivery when given appropriate fluid challenges.[20,24] Traditionally intravascular volume is assessed by static parameters (CVP and left atrial pressures) but more recently there is considerable interest in measuring dynamic parameters to improve accuracy.

Static measurement of intravascular volume Despite its limitations, a commonly used marker for the assessment of the preload is the CVP (right atrial pressure). The pulmonary artery wedge pressure (left atrial pressure) is usually monitored only in cardiac surgical cases or critically ill children with lung disease. If fluid challenges do not improve cardiac output, it means that inadequate fluid has been administered or that there is impaired cardiac contractility.

Dynamic assessment of intravascular volume Dynamic measurements evaluated include systolic pressure variation (SPV), pulse pressure variation (PPV) and stroke volume variation (SVV).[14,24] A difference of greater than 13% in maximum and minimum values during inspiration and expiration has been shown to be highly sensitive and specific in identifying hypovolemic patients who are fluid responsive. These values are however sensitive only in the sedated ventilated patients in sinus rhythm. In non-ventilated patients, a fall in CVP by 1 mm Hg during inspiration is a predictor on the need for additional fluid challenges. In ventilated patients, a collapsibility of the inferior vena cava greater than 12% during respiration has been shown to predict response to fluid boluses.

Assessment of Tissue Oxygenation

A functional end-point for cardiac output is to assess whether there is adequate oxygenation of the tissues. The markers used to assess tissue oxygenation are the *mixed venous oxygen saturation* and the *blood lactate*.[14,20] The normal mixed venous oxygen saturation is 73% (65–75%) and the average arteriovenous oxygen saturation difference is 20–33%. An elevated blood lactate usually indicates anaerobic glycolysis in the skeletal muscles due to circulatory insufficiency. Elevated lactates are also seen in sepsis due to tissue dysoxia.[20] A mixed venous saturation below 60% is clearly abnormal and a value below 50% indicates a worse outcome. Normally, the serum lactate is below 2 mmoL/L. Serum lactate above 4 mmoL/L indicates worse outcome.

In circulatory insufficiency, blood supply to vital organs is maintained at the cost of perfusion to the skin and splanchnic areas. Splanchnic hypoperfusion can be identified by *sublingual capnometry* and *gastric tonometry*, and skin hypoperfusion can be identified by *transcutaneous CO_2 estimation*. Newer techniques like *orthogonal polarization spectroscopy* and *near-infrared spectroscopy*[14,20] attempt at direct assessment of microcirculation but are not yet in clinical use.

CONCLUSION

Monitoring is an important aspect of critical care and improves patient care. In recent years there has been an explosion in medical technology and it is now imperative that clinicians approach monitoring in a rational manner. The basic question an intensivist needs to ask is whether monitoring is justified and likely to improve outcome.[8,25] Clinicians are increasingly aware that monitoring should be done in a clinically appropriate manner, taking into account need, cost, accuracy and safety of monitoring techniques.

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CHAPTER 79

Approach to Shock in the Pediatric Intensive Care Unit

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GENERAL CONSIDERATIONS

Shock is defined as a state of circulatory dysfunction that results in failure to provide adequate oxygen and other nutrients to meet the metabolic demands of the tissues. This is usually due to a reduction in cardiac output, maldistribution of regional blood flow, or a combination of both factors. Rarely it may occur due to increased metabolic requirements or impaired oxygen utilization at the cellular level. Such cellular oxygen deficiency leads to altered metabolism and decreased energy production, which, if uncorrected, may result in death.

Everchanging metabolic demands of tissues are met with primarily by adjustments in the cardiac output, which is the product of stroke volume and heart rate. In infants and young children, it is mainly the increase in the heart rate which tries to maintain the cardiac output, whereas in older children (as in adults), stroke volumes can be efficiently increased to improve cardiac output, without significant change in the heart rate. Thus infants and young children are at high risk of decompensation at an earlier stage as compared to older children. Besides suitable modification of cardiac output, the metabolic demands of a particular organ can be met by augmenting the regional blood flow by appropriate changes in the vasomotor tome mediated through neurohumoral mechanisms. When such physiological changes fail to meet the metabolic requirements, shock ensues. In pediatric practice, shock is a common accompaniment of many disease states; however, the pathogenesis of shock varies depending upon the nature of disease. The different clinical forms of shock are briefly enumerated below—

- *Hypovolemic shock* results from decreased circulating blood volume commonly due to loss of fluids from the extravascular or intravascular compartment; it may also be due to third space fluid losses associated with the capillary leak syndromes.
- *Distributive shock* results from maldistribution of blood flow due to widespread abnormalities in vasomotor tone. Vasodilatation leads to venous pooling with decreased preload and shock ensues. Septic shock represents this type of shock. Other etiologies, like central nervous system injury, anaphylaxis and drug intoxication, may also result in distributive shock.
- *Cardiogenic shock* results from decreased myocardial contractility. It may occur in patients with congenital heart defects, in whom shock is preceded by congestive cardiac failure, or in children with previously normal hearts who have suffered hypoxic injury or metabolic derangements.
- *Obstructive shock* results from mechanical obstruction to venous inflow to the heart, as seen in cardiac tamponade, or to tight ventricular outflow as in pulmonary embolism.
- *Dissociative shock* occurs in conditions like methemoglobinemia and carbon monoxide poisoning where oxygen is not released from hemoglobin to the tissues, in spite of normal tissue perfusion.

The first three types of shock are quite common while the last two varieties are rather rare.

PATHOPHYSIOLOGY OF SHOCK[1]

Reduced cardiac output is the main factor in the evolution of shock. Hypovolemic shock results from a decrease in preload due to contraction of the intravascular volume as a result of blood or fluid loss. In septic shock, decrease in preload is the result of much more complex mechanisms. In sepsis, bacterial products interact with the reticuloendothelial cells to produce

a wide variety of mediators, which exert a potent effect on vascular tone and permeability leading to maldistribution of blood flow. Activated complement components promote leukocyte and platelet aggregation in capillaries, resulting in mechanical obstruction to blood flow. These changes in microcirculation which are the hallmark of septic shock also depress myocardial function, which further reduces cardiac output, as in cardiogenic shock. Thus, diminished cardiac output and resultant lowering of blood pressure trigger a series of changes that are characteristic of the clinical shock states.

Compensated Stage

With the onset of shock, the body tries to compensate for the reduced cardiac output by sympathetic discharge which leads to vasoconstriction, thereby increasing the heart rate and myocardial contractility. This results in improved cardiac output and blood pressure. However, if the basic condition leading to shock is not controlled quickly, continued sympathetic overactivity beyond a certain limit proves detrimental to the patient, precipitating the decompensated stage of shock.

Decompensated Stage

Increasing heart rate leads to reduced myocardial perfusion and excessive oxygen consumption, which results in lowering of cardiac output. Hence the very mechanisms which are compensatory in the early stage of shock prove to be detrimental at a later stage, perpetuating tissue ischemia, impairing cell function and ultimately resulting in cell death. Tissue ischemia releases biochemical mediators which exert potent effects on capillary endothelium and other cellular elements, thereby aggravating existing damage.

Cellular Response to Ischemia

Tissue ischemia with resultant lack of oxygen gives rise to anaerobic cell metabolism. Only 2 moles of adenosine triphosphate (ATP) are produced per mole of glucose, instead of 38 moles produced by aerobic metabolism. Cellular ATP levels fall leading to failure of energy-dependent processes. Anaerobic glycolysis with excess of lactate production and increased organic phosphates from ATP hydrolysis results in extracellular and intracellular acidosis. This leads to influx of sodium, calcium and water into the cell, and efflux of potassium out of the cell; this damages the cell membrane and further impairs cell-ion regulation. Such changes impair energy production and promote release of acid hydrolases, which in turn cause tissue inflammation and injury.

Chemical Mediators in Shock

In all types of shock, but particularly in septic shock, mediators play an important role in initiating and sustaining impairment in tissue perfusion.[2] These agents cause vasospasm, platelet aggregation and thrombus formation; they also increase capillary permeability, and promote maldistribution of blood flow.

A variety of arachidonic acid metabolites have been implicated as being modulators of shock. Thromboxane A_2 is the most important of these compounds. It is mainly formed by the platelets and also by vascular smooth muscle, lung and the spleen. It is a potent vasoconstrictor and has platelet aggregating thrombogenic properties. These effects further reduce blood flow in an already compromised microcirculation, producing extension of tissue ischemia and death. Vasoactive prostaglandin-F (PGF) alpha-2 is also formed by the platelets and is a potent vasoconstrictor. Prostacyclin is believed to neutralize the deleterious effect of thromboxane and is produced by healthy capillary endothelium. However, as the capillaries are damaged, insufficient prostacyclin is produced and hence the shock state is perpetuated. Leukotrienes are produced by different types of cells like leukocytes, macrophages and mast cells. They enhance capillary permeability, produce intense vasoconstriction and have a myocardial depressant action. Intrinsic myocardial depression exists in all types of shock, mediated through several hemodynamic mechanisms. Irrespective of these factors, a small peptide released from pancreatic acinar cells due to ischemia is known to exert a negative inotropic effect, and is named the myocardial depressant factor. This mediator depresses myocardial function even in the presence of normal coronary flow, preload and afterload. This factor also causes pancreatic ischemia, as well as depression of the reticuloendothelial system. Endogenous opiates, most widely implicated in the pathogenesis of shock, are released from the pituitary in response to stress.

CLINICAL APPROACH

In vulnerable clinical settings, one must suspect and watch for early signs of shock. Much before clinical signs manifest clearly, there may be early clues, raising a suspicion of shock. Disproportionate tachycardia and tachypnea indicates systemic inflammatory response and is a forerunner of impending sepsis. An increase in the difference between the core and skin temperatures, and postural hypotension may suggest impending shock. Subsequently typical clinical signs develop which consist of increasing tachycardia, increasing tachypnea, low or normal blood pressure, cool and mottled extremities, poor color and prolonged capillary refill, more than 2–3 seconds. In the early stage of distributive shock, patients may be febrile with a dry hot skin, and normal blood pressure often referred to as warm shock. Urine output is an excellent indicator of renal perfusion and must be monitored on an hourly basis. A depressed neurological state may ensue later. All the above-mentioned clinical signs must be periodically assessed; however, they have to be supplemented by appropriate biophysical and biochemical parameters.

Septic shock[2] is a clinical challenge for early diagnosis and prompt management. Though Gram-negative bacterial infections are more commonly the causative factors in the evolution of septic shock, Gram-positive bacterial infections as well as viral infections, parasitic infections (like malaria),

and even myobacterial and fungal infections may lead to septic shock in children. In fact, any infection in a vulnerable setting constitutes a potential threat to develop into septic shock. It is the sound knowledge of interactions between host factors and infections that guide a clinician to anticipate the outcome in a given infection. If an infection, instead of localizing, threatens to spread, a competent host develops a systemic inflammatory response syndrome (SIRS). SIRS is a measure of a counter-regulatory process, clinically evident by disproportionate tachycardia and tachypnea. This stage represents early sepsis. If infection further worsens, the counter-regulatory mechanisms fail to maintain the body's homeostasis. This corresponds to a stage of severe sepsis. On further deterioration, organ failure ensues and this heralds the development of septic shock. In unfavorable conditions, a patient may pass through these stages rapidly within 12–24 hours, giving little time for action. Hence clinical anticipation and early monitoring are key factors for successful management.

For the sake of understanding, three distinct phases (early sepsis, severe sepsis and septic shock) may be defined; each phase however overlaps the other, and there are no clinical or investigatory parameters for their precise diagnosis.[3] It is the continuous monitoring of vital parameters together with periodic biochemical monitoring that predicts the trend in a given disease state. A single record of any parameter is of much less significance that the trend observed over a period of time. Besides continuous display of heart rate, respiratory rate, core and skin temperatures, and noninvasive blood pressure readings, arterial oxygen saturation, and end-tidal PCO_2 monitoring help in optimum management. Central venous pressure (CVP) monitoring helps in the infusion of adequate amount of fluids especially in septic shock. Children with septic shock need very large amounts of fluid and are in constant danger of both under- or overperfusion, in the absence of proper monitoring facilities. Sophisticated monitoring may entail the study of metabolism at cellular level, and assessing both oxygen delivery and consumption.[4]

MANAGEMENT

Early rapid infusion of fluids to replenish the intravascular volume, often decides the ultimate outcome of a patient in shock.[5] In septic shock the source of sepsis should be promptly identified and eradicated. The earlier this is done, the better the prognosis. Empiric use of antibiotics in patients where the nature of infection cannot be immediately proven is on the same principles as in adults.

Diagnosis of early shock should be followed by volume challenges of at least 20 mL/kg body weight of Ringer lactate. If this produces improvement in vital parameters, then appropriate infusions are continued and the patient is monitored clinically. However, if there is no adequate improvement on such a challenge, then further infusions should be planned by CVP monitoring. Crystalloids are commonly used; they may be safely infused to an amount equivalent to 50% of circulating blood volume, beyond which point peripheral tissue and pulmonary edema may develop. Colloids like plasma, blood or dextran are administered under close monitoring, as they are likely to expand the intravascular space by a volume greater than that infused, and may cause circulatory overload. Dextran solutions have an advantage of improving microcirculation by decreasing RBC aggregation and improving oxygen transport; however, their administration should not exceed 20 mL/kg per day. In hypotensive patients dopamine may be required to augment cardiac output, whereas in low cardiac output states with normal blood pressure, dobutamine may be the drug of choice. Vasodilators may be indicated in the late stages of shock where vasoconstriction is the prominent feature. Cardiac failure and rhythm disturbances may need appropriate therapy.

If in spite of adequate replacement, hypotension and hypoperfusion persist, CVP monitoring alone may not suffice, and further invasive monitoring is often required to assess the right and left atrial pressures and cardiac output; however, this is not routinely required. In case of renal hypoperfusion, diuretics should be used only after adequate volume expansion.

Metabolic status including oxygenation should be periodically evaluated and adequate steps are necessary to correct abnormalities. Hypoxia at the cellular level is the key factor in the pathogenesis of shock, and hence adequate oxygenation is mandatory in every patient. Blood gas determinations should guide timely interventions, including mechanical ventilator support.

The use of corticosteroids in the management of shock is controversial. Though theoretically steroids are supposed to exert a beneficial effect through various mechanisms, controlled studies have not found statistically significant benefits, and hence no definite recommendations can be made. Many other drugs have been tried, like the opiate antagonist naloxone, and thyrotropin, but as yet these cannot be recommended for routine use. Future drugs used

Box 1: Resuscitation in shock

Goal of therapy—
- To maintain normal blood pressure and keep mixed venous O_2 saturation >70%

Management—
- Recognize poor perfusion—reduced urine output and mental status
- Maintain airway and secure vascular access
- Aggressive volume replacement—
  - Push 20 mL/kg body weight of isotonic saline in 20 minutes—if need be repeat two more pushes over next 40 minutes
  - If fluid refractory shock—establish central venous pressure and start dopamine
  - If fluid refractory and dopamine resistant shock—epinephrine for cold shock and norepinephrine for warm shock
  - If catecholamine-resistant shock—hydrocortisone

in shock would essentially antagonize the actions of the numerous chemical mediators involved in shock. Till then, early recognition, maintenance of a satisfactory circulatory and metabolic state, and above all, prompt eradication of the underlying pathology remain the mainstays of management (Box 1).

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CHAPTER 80

Hypertensive Emergencies in Pediatrics

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GENERAL CONSIDERATIONS

In children, severe hypertension is almost always secondary. In fact, primary hypertension is mild and asymptomatic. About 80% of children with hypertension have underlying kidney disease, two-thirds of them mesoparenchymal and one-third renovascular. Ten percent of patients suffer from hypertension due to coarctation of aorta or aortoarteritis of various etiologies. The remaining patients comprise of endocrinal disorders and other miscellaneous causes.

Hypertensive emergencies may occur in patients with known kidney disease. However, at times hypertension may be the only presenting feature, often manifesting with vague nonspecific symptoms that may suggest primary central nervous system (CNS), cardiovascular or ocular disease. Hence in any seriously ill child who presents with ill-defined encephalopathy (headache, vomiting, irritability and change in sensorium), cardiac failure, or visual disturbances of unknown etiology, the blood pressure must be recorded. Accurate measurement of blood pressure is difficult in children and demands a proper size cuff, correct technique and patience on the part of the clinician. As the blood pressure is markedly elevated in hypertensive emergencies, a small error in the blood pressure recording does not change the interpretation or the management.

It is the sudden rise in the blood pressure that presents as an emergency, rather than chronically elevated blood pressure which has fewer symptoms. The child may present with convulsions and demonstrate various neurological abnormalities mimicking intracranial infection. Fundus examination may show evidence of papilledema or retinal hemorrhages. Sudden onset of left ventricular failure, especially in the presence of overhydration may be a manifestation of acute glomerulonephritis and may be mistaken for myocarditis or bronchopneumonia.

MANAGEMENT[1-3]

The main aim of therapy is to reduce the blood pressure to a safe level, control various complications like seizures, cardiac failure and airways obstruction, and treat the primary cause when feasible. Reduction of blood pressure should be achieved over 3–4 days to a level of 95th percentile appropriate for the age. A sudden precipitous fall in blood pressure may be associated with development of neurological signs and impairment of cerebral and renal blood flow. Several drugs are available for prompt reduction of blood pressure. Diazoxide and labetalol are not easily available, and nifedipine is the drug most often used in our setup. Though sublingual administration is known to lead to a sudden fall in blood pressure, in our experience it occurs rarely. Sodium nitroprusside is an excellent drug for continuous infusion; it is extremely potent and needs careful titration of the dose by constant monitoring. Hydralazine is another drug, but is rather slow in action. In case of accompanying fluid overload, diuretics like furosemide can be used; otherwise, diuretics may in fact be harmful as they may lead to volume depletion and hypotension. Dosage of drugs commonly employed in the treatment of hypertensive emergencies are given in Table 1.

Supportive measures include control of seizures by diazepam 0.3 mg/kg per dose, and antifailure treatment in case of cardiac failure. Surgical intervention may be necessary at times. Maintenance therapy for hypertension can be continued orally.

Table 1: Drugs commonly used (with route of administration and dosage) for treatment of hypertensive crisis in the pediatric age group

Drug	*Route of administration*	*Dosage*
Nifedipine	Sublingual	0.5 mg/kg every 4–6 hours
Sodium nitroprusside	IV infusion	0.5 µg/kg per minute
Labetalol	IV	1–3 mg/kg
Diazoxide	IV	1–5 mg/kg every 4–6 hours
Hydralazine	IV	0.2 mg/kg every 4–6 hours
Furosemide	IV	2–5 mg/kg

Abbreviation: IV, intravenous.

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CHAPTER 81

Heart Failure in Neonates and Children

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GENERAL CONSIDERATIONS

Cardiac failure is a state in which the heart cannot maintain adequate output to sustain metabolic demands of the body. In the early stages, the heart tries to maintain optimum output by physiological adjustments; however, after a certain point, compensatory mechanisms fail, and decompensated stage of cardiac failure ensues. Clinical manifestations vary a great deal between neonates and older children. No age is exempted from cardiac failure, but the etiological factors are so diverse in the different age groups that prompt recognition of cardiac failure and diagnosis of its etiology, often pose a challenge to the clinician. Moreover, the majority of these patients present as medical emergencies, with very rapid decompensation. This is due to the limitations of physiological compensatory mechanisms in children. Unlike adults, where stroke volume can be modified to a considerable extent by appropriate changes in myocardial contractility, preload and afterload, in children it is mainly changes in the heart rate that try to maintain cardiac output, without much change in the stroke volume. However, increase in the heart rate beyond an optimum level, in fact, results in poor coronary filling, and increased oxygen consumption leading to early decompensation. Thus early recognition of cardiac failure is far more important in young children.

In our experience, 10% of patients in any pediatric intensive care unit (ICU) manifest with significant cardiac problems. Though congenital defects and acquired heart diseases presenting with cardiac failure are common to all age groups, certain conditions predominate in specific age groups. Besides congenital defects like hypoplastic left heart, transposition of the great vessels and large left to right shunts, birth asphyxia is an important cause of cardiac failure in newborns. Occasionally, a baby is born with hydrops fetalis is as a result of cardiac failure due to severe anemia caused by isoimmune hemolytic disease. Severe anemia in the newborn may also be caused by fetomaternal transfusion, hemorrhage due to birth injury or a bleeding diathesis. In infants and young children, cardiac failure may result from large left to right shunts, endocardial fibroelastosis, cardiomyopathy, viral myocarditis and hypertension, including coarctation of the aorta. In older children above 5 years of age, rheumatic heart disease is a major cause of cardiac failure in our country. Other important conditions include infective endocarditis, viral myocarditis, diphtheritic myocarditis and pericardial effusion due to tuberculosis or other infections. Acute hypertension often presents with cardiac failure in this age group. Cor pulmonale, thyrotoxicosis and beriberi, are rare in children.

CLINICAL FEATURES[1]

Newborns and infants present with varied and vague symptoms that are often unrelated to the cardiovascular system. Poor feeding, vomiting, diarrhea may be initial symptoms while restlessness, excessive sweating and crying may offer clues to the diagnosis of cardiac failure. Tachypnea, chest retractions and tachycardia are invariably present. Hepatomegaly is a constant feature, though tenderness and the hepatojugular reflux are difficult to elicit. Normally, the liver is palpable in newborns and young infants, and has a clearly defined edge. In case of cardiac failure, the liver edge becomes rounded and is a good clinical pointer to a pathological liver. Edema of feet is often absent. Marked tachycardia, gallop rhythm and murmurs, if present, are commonly observed clinical signs.

In older children, symptoms and signs are similar to those seen in adults, and hence easily detected. Breathlessness, edema on dependent parts, right hypochondrial pain, and oliguria are the classical symptoms. Besides tachycardia and tachypnea, a tender, enlarged liver with a positive hepatojugular reflux, cardiomegaly, basal crepitations in the lungs, soft heart sounds and murmurs, if any, are the characteristic clinical signs. Signs of cardiogenic shock may ensue at any stage.

INVESTIGATIONS[1]

In newborns and young infants, mild cardiomegaly is difficult to assess radiologically. Echocardiography (ECG) needs proper-sized chest leads, and interpretations are essentially age-dependent. Two-dimensional ECG with Doppler study is very useful in delineating anatomical defects, as well as assessing the functional state of various chambers and valves. Vegetations can be picked up easily in cases of active rheumatic carditis as well as in infective endocarditis. Other relevant investigations include serum electrolytes, acid-base balance and oxygenation status.

MANAGEMENT[2-5]

Cardiac failure is an emergency which especially in infants and young children needs prompt management. Nonpharmacological measures are as important as drug treatment. A proper position (ideally propped up) is comfortable for older children, but infants may have to be managed even on the mother's lap. Humidified oxygen is given by a hood in an infant, at the rate of 8–10 L/minute; this may be administered by mask or nasal prongs in older children. Adequate sedation may be necessary at times in young children, either with chloral hydrate (20–25 mg/kg per dose orally) or in very sick infants with pulmonary edema, even with morphine (0.1 mg/kg per dose subcutaneously). Adequate hydration and nutrition need to be maintained by suitable methods, either orally or intravenously. Salt-restricted diet with sufficient calories and appropriately restricted fluids may have to be planned to meet the increased energy requirements, without overloading the child with salt and water.

Cardiac output may be increased by using inotropic drugs combined with diuretics and vasodilators as and when necessary. Digoxin is an important drug in the control of cardiac failure.[2,3] In pediatric patients, rapid digitalization (0.04–0.05 mg/kg) over 24 hours is generally required; however, in certain conditions in older children, slow digitalization over a week may be ideal. Later, a maintenance dose of 0.01 mg/kg per day is administered. Other inotropes like dopamine and dobutamine are used in cardiogenic shock, asphyxia and postsurgical conditions. Diuretics like furosemide (1–2 mg/kg per day), thiazides (1–2 mg/kg per day) and spironolactone (1–2 mg/kg per day) are used judiciously in combination with digoxin, starting with a low dose and titrating the same as per the clinical state. Vasodilators like captopril (0.5–2 mg/kg per day) may be useful in cases of pulmonary edema due to mitral or aortic regurgitant lesions, as well as in postoperative patients with cardiac failure. Precipitating factors like anemia, electrolyte disturbances, arrhythmias and infective endocarditis must appropriately be treated for successful management of cardiac failure.

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CHAPTER 82

Acute Respiratory Failure in Children and Hyaline Membrane Disease

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ACUTE RESPIRATORY FAILURE IN CHILDREN[1]

Respiratory failure, either impending or manifest, is a significant threat in many patients in pediatric practice. In our experience, 20% of patients in a pediatric ICU are admitted for primary respiratory emergencies, though in many other conditions, secondary respiratory problems ensue, needing prompt respiratory care. Such diseases include cardiac failure, peripheral nervous system disorders as in the Guillain-Barré syndrome, poliomyelitis, myopathies, central nervous system (CNS) disorders and shock states. Thus, respiratory dysfunction is a common denominator in many, pediatric ICU patients.

Common pulmonary diseases presenting with respiratory failure include pneumonia, severe asthma, acute bronchiolitis,[2] pulmonary edema, and the croup syndrome. Other problems causing acute respiratory failure include foreign body obstruction and hydrocarbon poisoning. Epiglottitis causing upper respiratory obstruction is rarely seen in our country. The important causes of acute respiratory failure in the pediatric age group are listed in Box 1.

Neonates may present with hyaline membrane disease, meconium aspiration, persistent pulmonary hypertension, congenital malformations, like diaphragmatic hernia and lobar emphysema, as well as pneumonias, birth asphyxia and pulmonary hemorrhage. Extrapulmonary conditions include CNS infections and cardiac diseases. The important causes of acute respiratory failure in neonates are given in Box 2.

Acute respiratory failure in terms of arterial blood gas estimation is defined as arterial carbon dioxide tension ($PaCO_2$) more than 50 mm Hg and/or arterial oxygen tension

Box 1: Important causes of acute respiratory failure in the pediatric age group

- Pulmonary causes—
  - Pneumonia
  - Severe asthma
  - Acute bronchiolitis
  - Pulmonary edema
  - The croup syndrome
  - Obstruction by foreign body
  - Epiglottitis causing upper respiratory obstruction
- Nonpulmonary causes—
  - Cardiac failure
  - Neuromuscular disorders, e.g. Guillain-Barré syndrome, myopathies
  - Central nervous system disorders, e.g. poliomyelitis
  - Shock states

Box 2: Important causes of acute respiratory failure in the neonates

- Pulmonary causes—
  - Hyaline membrane disease
  - Persistent pulmonary hypertension
  - Congenital malformations, e.g. diaphragmatic hernia, lobar emphysema
  - Pneumonia
  - Pulmonary hemorrhage
  - Birth asphyxia
- Extrapulmonary causes—
  - Central nervous system infections, e.g. neonatal tetanus
  - Cardiac diseases (generally congenital heart disease)

(PaO_2) less than 55 mm Hg, while breathing room air. It may be clinically classified into pump failure (disorders of mechanics of respiration), and lung failure (diseases of airways and lung parenchyma). Pump failure is characterized by an increase in $PaCO_2$ and a fall in PaO_2; whereas lung failure is characterized by a decreased PaO_2 with a normal or low $PaCO_2$. Later in the natural history of lung disease, the occurrence of alveolar hypoventilation or of respiratory muscle fatigue can cause a gradual rise in the $PaCO_2$. The above classification has an implication both in relation to etiology and management. Thus an increase in $PaCO_2$ in pump failure may well be an indication for initiating mechanical ventilator support. On the other hand, a decrease in PaO_2 with a low $PaCO_2$ may respond to an increase in the fraction of inspired oxygen (FiO_2), if hypoxia is chiefly due to a ventilation-perfusion (V/Q) mismatch produced by lung disease. If however a decrease in PaO_2 is chiefly due to a right to left shunt within the lungs, increase in FiO_2 will not produce a significant increase in the PaO_2. Ventilator support will be required in these patients, as also in those who ultimately show a progressive increase in the $PaCO_2$.

Pathophysiology involves five mechanisms of hypoxemia—reduced PiO_2 (as in high altitude), hypoventilation, V/Q mismatch, shunt and a diffusion abnormality. (It is least important as at sea level, there is rarely a problem of diffusion as there is enough time for red blood cells to exchange gases and even in case of diffusion abnormality, it is coexistent V/Q mismatch and shunt that is more responsible for hypoxemia.) Hypoxemia in hypoventilation is accompanied with normal A-a difference and a high $PaCO_2$. V/Q mismatch can be differentiated from shunt as hypoxemia in V/Q mismatch can be easily corrected by a slight increase in inspired O_2 concentration while hypoxemia in shunt is not corrected easily by oxygenation and even an FiO_2 of 1 may only modestly increase PaO_2 in a shunt.

In newborns and young children respiratory failure can develop rapidly due to various unfavorable anatomical and physiological factors, like poor compliance of the lungs, easy blockage of air passages, immaturity of the cough reflex and the higher centers, and poor respiratory reserve with early fatigability of respiratory muscles.

Clinical Features

It is important to realize that respiratory distress may occur in the absence of respiratory disease or failure. Conversely, respiratory failure may be present without respiratory distress as in patients with muscular weakness or CNS depression. Diseases, like encephalitis and Reye's syndrome, as well as diseases causing metabolic acidosis may present with hyperventilation, which may be mistaken for respiratory distress. Apnea may be the manifestation of respiratory failure in neonates. Respiratory distresses, with activity of accessory muscles of respiration, along with chest retractions, stridor, grunting or wheezing, are important clinical manifestations. Symptoms and signs of hypoxemia manifested by restlessness, confusion, hypotonia and cyanosis may supervene. Muscle fatigue may be evident by paradoxical breathing and see-saw movements of the chest and upper abdomen. Convulsions, shock and cardiorespiratory failure ultimately supervene.

The clinical features of neonatal tetanus are characterized by difficulty in suckling and swallowing due to spasm and rigidity of the muscles of the face and of deglutition. Risus sardonicus with the characteristic tetanus fancies is diagnostic of the disease. In neonatal tetanus, skeletal and truncal rigidity is quickly followed by convulsive seizures. Breathing is impaired; atelectasis is frequent and acute hypoxemic respiratory failure results. Death generally results from cardiorespiratory failure.[3]

Diagnosis

The clinical diagnosis of respiratory failure should be supplemented by relevant investigations. Arterial blood gas estimation defines the type and severity of respiratory failure. This can be further monitored by noninvasive parameters, like SaO_2, transcutaneous PO_2 and capnography. These noninvasive methods certainly have limitations, but are very useful for defining the trends in progress. Chest X-ray is helpful in evaluating the cause, progress and complications of respiratory disease. Ultimately, cardiac, CNS and other organ dysfunctions need to be monitored by appropriate tests.

MANAGEMENT

Pump failure is rather easy to manage. Mechanical ventilation is required with an increasing $PaCO_2$ due to ventilatory failure. In our experience, patients with ventilatory failure who, to start with, have normal lungs, tolerate prolonged mechanical ventilation for several weeks without any complications. We have had a newborn with congenital amyelinosis, and a 6-week-old infant with severe poliomyelitis who, despite being on mechanical ventilation for longer than 12 weeks, presented no problems in management. However, lung failure is a challenge to the clinician.[4] It is in this type of failure that skilful management may change the outcome, because in lung disease, there exists a high risk of inflicting further damage by the use of both high inflation pressures and high concentrations of inspired oxygen. The aim of management is to maintain blood gases and acid-base status within the optimum range. This is primarily done by adequate oxygenation and ventilation. Humidified oxygen is administered at suitable flow rates depending on the method of delivery used—be it by oxygen hood, mask or nasal prongs. In pediatric practice, Venturi mask is rarely required as we do not encounter patients with chronic respiratory disease, dependent on the hypoxic central drive. Except in preterm neonates, where FiO_2 needs to be stringently monitored, short-term high oxygen concentrations are well tolerated.

In children, ventilatory settings depend on the age and body size. Table 1 details the standard ventilator settings used in infants and children. However, these may be modified depending on the disease and its pathophysiology. Pressure-limited time-cycled ventilation is ideal for newborns and

Table 1: Standard ventilator settings in neonates and older children

Settings	*Newborns and infants*	*Older children*
Tidal volume	10 mL/kg	10 mL/kg
Respiratory rate	25–30/min	20/min
Peak inspiratory pressure	15–20 cm of H_2O	20–25 cm of H_2O
PEEP	2 cm of H_2O	2 cm of H_2O
Inspiratory: Expiratory ratio	1:2	1:2

Abbrreviation: PEEP, positive end-expiratory pressure.

infants, whereas older children require volume-control ventilation. The peak inspiratory pressure should not exceed 15–20 cm H_2O in neonates and infants, and 20–25 cm H_2O in older children. Positive end-expiratory pressure (PEEP) is often used in children to improve oxygenation, though too much PEEP is harmful. Square wave pressure generation with prolonged inspiration time may be ideal to improve oxygenation in acute lung disease.

Continuous positive airway pressure is an intermediate method between mechanical ventilation and spontaneous breathing. It is normally delivered through an endotracheal tube, though it may also be employed to some extent through a nasopharyngeal tube, or even through a tight-fitting mask in small children. Specific treatment of the underlying disease and management of dysfunction of other organ systems are as important as the primary management of respiratory failure.

Orotracheal intubation with proper length and size of endotracheal tube is a prerequisite. Nasotracheal intubation is technically difficult in small children, and its long-term use is known to be associated with higher incidence of middle ear infections. In children, mechanical ventilation is required for a short time in most cases. The size of the endotracheal tube should be such as to allow a small leak under positive pressure. Tight-fitting tubes with a tight seal may lead to tracheal stenosis. At the same time, too large a leak may hamper adequate ventilation. The formula of [(16 + age in years) ÷ 4] is a useful guide for determining the size of the endotracheal tube. An endotracheal tube of a small diameter in pediatric patients is prone to get blocked by thick secretions, and hence proper humidification of the respiratory tract is an important yet often neglected aspect of management. On the other hand, enthusiastic over humidification may lead to absorption of considerable amount of water. Frequent suction by sterile techniques is necessary in many ventilated children. Bag and tube ventilation with 100% oxygen prior to suctioning prevents hypoxemia. Suction should be done whilst withdrawing the catheter gradually over 8–10 seconds. Between each suctioning, 100% oxygen is administered by bagging. An end-hole catheter is preferred to a side-hole one, to avoid trapping of respiratory mucosa. Development of bradycardia is indicative of hypoxemia and suctioning must be immediately stopped, and the patient ventilated with 100% oxygen. Infection must be prevented by proper asepsis including hand washing, use of disposables and proper sterilization of equipments including ventilators. Delicate parts of the ventilator circuits, like transducers, are chemically sterilized in alcohol. Colonization of ventilators, humidifiers and endotracheal tubes by Gram-negative organisms, including pseudomonas infection, is a major problem in management. Scrupulous attention must be paid to prevent infections. Respiratory tubings must be changed every 2–3 days, or more frequently in the presence of colonization.

Patients needing mechanical ventilation often require some form of sedation or muscle relaxants. We use pancuronium bromide in the dose of 0.15–0.2 mg/kg intravenously, as an initial dose and repeat this every 2–4 hours as required. Paralyzing patients for prolonged periods may cause a gradual fall in the compliance of the lungs, and sudden accidental disconnection of the ventilator may be fatal in a paralyzed child.

HYALINE MEMBRANE DISEASE (RESPIRATORY DISTRESS SYNDROME)[5]

Hyaline membrane disease occurs primarily in premature neonates. Its incidence is inversely proportional to the gestational age—60% to 80% in infants less than 28 weeks of gestation, and rare in term babies. The incidence is also increased in infants born to diabetic mothers and in those delivered by cesarean section.

Absence of surfactant results in high surface tension and keeps the alveoli atelectatic. Along with atelectasis, formation of hyaline membrane and interstitial edema make the lungs poorly compliant. High compliance of the chest wall in preterm infants offers less resistance against the tendency of the lungs to collapse. This results in poorly ventilated, though well-perfused alveoli, leading to hypoxia. Poor lung compliance and alveolar hypoventilation, increased dead space, small tidal volumes and extra work of breathing, all contribute to hypercarbia. A combination of hypoxia, hypercarbia and acidosis results in pulmonary vasoconstriction leading to right to left shunting, reduced pulmonary flow and ischemic injury to alveolar cells, thus worsening the vicious cycle.

Clinical presentation occurs early at birth, or within a few hours after birth, with tachypnea, chest retraction and cyanosis. This may progress over the next 24–48 hours to cause severe hypoxic injury leading to shock, hypotension, myocardial failure and renal dysfunction. Persistent hypoxemia in a typical setting, with diffuse lung infiltrates on chest X-ray, clinch the diagnosis of hyaline membrane disease. Pulmonary infections are difficult to exclude. Complications, besides acute respiratory failure and shock, include air-leak syndromes and shunting through a patent ductus and foramen ovale.

Management is aimed at improving oxygenation and reducing hypercarbia and acidosis by proper oxygenation and ventilation. Artificial surfactant can be instilled into the air passages through the endotracheal tube, which helps in reverting early pathological changes. Other drugs may be necessary to deal with accompanying problems—tolazoline

for persistent fetal circulation, aminophylline and doxapram to counter respiratory depression.

Prevention of hyaline membrane disease is possible by administering steroids to mothers 24–48 hours prior to delivery, especially before 32–34 weeks of gestation, trying to prevent preterm labor, and controlling maternal diabetes throughout pregnancy.

Surfactant Therapy

Exogenous surfactant therapy is widely used in preterm neonates with respiratory distress syndrome (RDS) and it is increasingly used in other respiratory conditions as well. There are two types of surfactants—natural and synthetic. The predominant and most efficient phospholipid in these products is DPPC (dipalmitoylphosphatidylcholine). However, DPCC adsorbs very slowly to the air-liquid interface.[6] Its adsorption is enhanced by other lipids and proteins contained in these products, including four major apoproteins—SP-A, SP-B, SP-C and SP-D.[6] They provide defense against inhaled pathogens. Among them SP-A is most efficient in regulating lowering of surface tension. None of the presently available preparations contain SP-A. Synthetic surfactants lack many of the components of natural surfactant.[7] Use of natural surfactants is preferred, though it needs refrigeration for storage. Synthetic surfactant is available in lyophilized form, can be stored at room temperature and reconstituted with sterile water before use.

While use of surfactant in preterm neonates is well established, there used to be a debate over timing of its use and number of doses required. However, in recent times, such a controversy is settled. In a neonate at risk of developing RDS, prophylactic use of surfactant immediately after stabilization is preferred to "rescue" therapy employed after development of RDS, even though such practice may result in the use of surfactant in a small number of neonates who may not have required it.[8,9] In those neonates who do not receive prophylactic surfactant therapy, early administration before 2 hours of age has better outcome than at later age. In patients who demonstrate good response to the first dose but deteriorate after some time, multiple doses are administered—3 to 4 doses over the first 72 hours. Such a strategy has proved to be useful.[8,9]

Current evidence suggests that surfactant administered through double-lumen endotracheal tube or a catheter passed through suction valve appears to be more effective and minimizes related adverse effects (including hypoxia) as compared to administration through the use of a simple catheter or side-port.

Adverse effects are few and not serious. Long-term follow-up of these neonates who receive surfactant is reassuring.

With the knowledge that surfactant deficiency occurs in many acquired disorders leading to acute lung injury, surfactant has been tried in such diseases with varying benefits.[8] Evidence suggests that preterm neonates with bronchopulmonary dysplasia and prolonged mechanical ventilation also experience surfactant dysfunction; however, exogenous surfactant therapy beyond the first week of life has not been well studied. Surfactant replacement therapy has been studied for use in other respiratory disorders including meconium aspiration syndrome and pneumonia.[8] Commercial surfactant preparations currently available are not optimal, given the variability of surfactant protein content and their susceptibility to inhibition. Further progress in the treatment of neonatal respiratory disorders may include the development of "designer" surfactant preparations.

Recently, natural exogenous surfactant replacement has been used in experimental models and clinical trials for the treatment of severe respiratory syncytial virus (RSV) disease. It has been shown that surfactant therapy improves gas exchange and respiratory mechanics and shortens the duration of ventilatory support and intensive care unit stay in infants with severe RSV-induced respiratory failure.

There is strong evidence that alterations in the pulmonary surfactant system play an important role in the pathophysiology of lung disease, including acute respiratory distress syndrome (ARDS). Although it is still unclear whether mortality and morbidity of ARDS will be reduced, surfactant replacement therapy has been shown to improve oxygenation and improve lung compliance, and decrease need for ventilator support. Further studies will also be needed to elucidate the optimal timing and dosage regimen for different disease processes. Some evidence supports the measurements of surfactant protein levels as markers for predicting the onset and outcome of ARDS and perhaps providing a window for early treatment of patients at risk to develop ARDS. Continued investigation into the role of surfactant in the immune regulation of the lung may also provide additional information to support the efficacy of surfactant replacement in lung disease.

However, meta-analysis of various trials has shown that exogenous surfactant administration has proven inconsistent as a therapeutic modality for patients with ARDS. This is because of severity of the injury at the time of treatment and because of variable surfactant preparations, dosing regimes, and delivery methods used in the different trials. Moreover, with the recognition that surfactant also plays an important role in host defense, the future for surfactant therapy is exciting.

In summary, role of surfactant is well established in preterm neonates suffering from RDS and it has now been a standard therapy to institute prophylactic therapy. However, its use in other conditions has met with varying success and at present cannot be recommended as a standard form of treatment. Its benefit to improve host defense may find favorable indications in future.

High Frequency Ventilation

High frequency ventilation (HFV) is a form of mechanical ventilation that uses small tidal volumes, sometimes less than anatomical dead space and extremely rapid ventilatory rates. Inherent too many modes of HFV are the small pressure swings during the respiratory cycle, which allow for higher mean airway pressures than those safety achieved with conventional mechanical ventilation (CMV). This has

the potential to reduce lung injury by limiting volutrauma, whereas maintaining bigger lung volumes at end-expiration may reduce atelectrauma. HFV has an ability to provide adequate gas exchange using lower proximal airway pressures in the lung already injured by barotraumas and volutrauma. It also enables preservation of normal lung architecture, even when high mean airway pressures are required. Normally efficient gas exchange depends upon adequate alveolar volume ($V_A = V_T - V_D$). It is quite perplexing and intriguing that tidal volume as small as anatomical dead space used in HFV can provide effective gas exchange.

The increasing understanding of the pathogenesis of acute lung injury, including concepts such as volutrauma, barotraumas, oxytrauma and atelectrauma has led to a renewed interest in the role of HFV in lung-protective ventilation strategies.

There are three types of HFV—high frequency positive pressure ventilation produced by conventional or modified CMVs operating at rapid rates, high frequency jet ventilation (HFJV) that delivers high velocity jet of gas into airways and high frequency oscillatory ventilation (HFOV) produced by a device that moves gas back and forth through airway opening.[10] HFJV and HFOV enhance both distribution and diffusion of gases. HFO is the only mode with an active expiration phase. This characteristic, combined with superior gas conditioning, may make HFO a promising ventilatory strategy for adults. Although a significant amount of data exists in the literature to support the application of HFO in infants and children who have acute respiratory failure, clinical data on the use of HFO in adults is only now emerging.

High frequency oscillatory ventilation is a new mode of ventilation using lung protective strategy and the safer use of mean airway pressure that is higher than that generally used during CMV. HFOV can achieve oxygenation and ventilation while maintaining maximal lung recruitment on the deflation limb of its pressure-volume curve.[11] The primary theoretical advantages of HFOV over CMV in the management of acute lung injury are that HFOV allows adequate alveolar ventilation with minimal peak-trough pressure changes, provides lung recruitment, and avoids end-inspiratory over distension of the relatively compliant nondependent lung. Taken together, the results of studies in animals, preterm and term neonates, and older pediatric patients reveal that an open-lung strategy, with the goal of a high end-expiratory lung volume is safe and superior to CMV in both the short term (rapidly improved oxygenation and/or ventilation) and long term (lower incidence of chronic lung disease).[11] The improved long-term clinical outcomes on HFOV are presumably because of less ventilator-induced lung injury. As experience with HFOV in older patients grows, ventilator technology matures, and understanding of the pathophysiology of ARDS deepens, it is likely that HFOV will find widespread use for the management of respiratory failure caused by acute lung injury in patients from preterm neonates to adults.

Full potential of HFV is yet to be realized in spite of 20 years of intensive studies. In air leak syndromes, including pulmonary interstitial emphysema and bronchopleural fistula, HFV improves outcome.[11] In congenital diaphragmatic hernia or pulmonary hypoplasia, its benefits are not clear. In seemingly intractable respiratory failure, studies suggest that HFOV is a better rescue therapy and also decreases the requirement of extracorporeal membrane oxygenation. In neonates with RDS, earlier trials with HFV have been contradictory but later trials are encouraging, especially along with the use of surfactant.[11]

Standard guidelines for use of HFV in neonates and older children are yet not available. Most clinical guidelines have been arbitrary and heavily depend upon experience, biases and, at times, idiosyncrasies of authors. Many different systems are in use all over the world and each HFV system is different in its functioning. There is no clear standard of practice.

High frequency ventilation has its own problems. As HFV is known to produce higher end-tidal volumes at lower proximal airway pressures, it can lead to an increasing auto PEEP. In many trials, pulmonary leaks increased in HFV as compared to CMV. Also, it is difficult to adjust the tidal volume so that there are neither underdistension and atelectasis of alveoli nor overdistension of alveoli.[11] Close observation and repeated X-rays of the chest may be necessary to determine if the lungs are inflated to the right extent. Even so, it is difficult to monitor lung volumes at the bedside.

Due to economic constraints and selected indications, we have had little experience with HFV. Outcome of preterm neonates with RDS has considerably improved with the use of surfactant. However, in our experience, conventional ventilation in RDS generally suffices and the need for HFV is not commonly felt.[12-14] In older children presenting with ARDS, who fail to improve on conventional ventilation strategies, the availability of HFV would perhaps make a difference.

In summary, HFV looks to be an exciting and useful form of ventilation. However, indications for its use are limited to select few patients and it is not yet standardized.

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CHAPTER 83

Fluid and Electrolyte Disturbance in the Critically Ill Child

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INTRODUCTION

Infants and children contain higher amounts of body water and electrolytes per kg body weight as compared to adults. Immaturity of renal function, particularly in early infancy, and increased vulnerability to dehydration and electrolyte disturbances, make the management of fluid and electrolyte imbalance an integral part of pediatric intensive care.

ENTERAL VERSUS PARENTERAL THERAPY

Though the enteral route is most physiological and ideal, intravenous (IV) fluid and electrolyte administration is imperative in almost every pediatric intensive care unit (PICU) patient for a variety of reasons. In a normal preterm neonate, the gastrointestinal (GI) tract needs to be rested for the first few days, till it stabilizes and starts functioning optimally. Also in every serious illness, the GI tract and the skin are always sacrificed in preference to more important vital organs, and hence the need for IV fluid therapy at least till the acuity of illness peaks off. Persistent vomiting, respiratory distress and risk of aspiration are additional factors necessitating IV therapy so as to prevent and rapidly treat significant dehydration and dyselectrolytemia. With the advent of several devices like butterfly scalp-vein needles, intracaths, and infusion syringes and pumps, fluids can be infused in any desired composition and concentration at any given speed, at any age over any period of time. Though IV fluid therapy is no longer a difficult technique, it should never be taken lightly as it carries the risk of infection, thrombophlebitis, overloading and cardiac failure.

NORMAL REQUIREMENTS[1-3]

On day one of life, a newborn needs 50 mL/kg of body weight of fluids per day, increasing on every subsequent day by 10 mL/kg, to reach 100 mL/kg of body weight per day by the 4th or 5th day. Till 1 year of age, or up to 10 kg of body weight, fluid requirements are constant at the rate of 100 mL/kg per day. Between 10 and 20 kg of weight, fluid requirements are computed at 100 mL plus 50 mL/kg per day for each kg beyond 10 kg weight, and subsequently over 20 kg body weight as 1,500 mL plus 20 mL/kg per day for each kg of body weight. Sodium and potassium are the two major electrolytes concerned with fluid therapy, though calcium and magnesium also play a role, especially in sick infants and children. A normal newborn is not able to handle electrolytes efficiently during the first 3–4 days, and should not be given supplements of sodium or potassium. There after, 2–4 mEq/kg per day of both the electrolytes are sufficient as maintenance requirements, spread uniformly over 24 hours. Potassium should never be infused in a concentration more than 4–60 mEq/L of fluid, even in the presence of normal renal function. Hyperosmolar solutions containing higher dextrose concentrations (more than 10–12.5%) are particularly harmful in small children. Similarly, in neonates and young infants, the rate of the dextrose infusion should be maintained constant at 5–6 mg/kg per minute so as to avoid hypoglycemia or hyperglycemia.

PATHOLOGICAL STATES

Dehydration

Acute diarrhea is the most common condition leading to dehydration in pediatric patients; other causes of dehydration

include persistent vomiting, polyuria or a diminished intake. Depending on the severity of dehydration, the deficit to be replaced may amount to 50, 100 or even 150 mL/kg per day of total fluids during infancy; further ongoing losses may also have to be replenished. Based on the type of fluids lost as in diarrhea, or vomiting, the electrolyte composition of infusion fluids needs to be modified. Commercial preparations like isolyte P contain a balanced composition of electrolytes. If these are not available, combinations of dextrose saline with required amounts of potassium chloride and sodium bicarbonate may be administered according to the need. In the majority of infants with diarrhea, dehydration is accompanied by hyponatremia, hypokalemia and metabolic acidosis, while in patients with vomiting, a hypochloremic metabolic alkalosis exists. In diabetic coma, dehydration may be accompanied by ketoacidosis, hyponatremia and hyperkalemia. In capillary leak syndromes as in septic shock, due to third space losses, dehydration may coexist with increased total body water.

Hyponatremia is common in many diseases such as pneumonia or meningitis. Even when the primary disease is not serious, hyponatremia may endanger life due to resultant brain edema. Hence, it is important to recognize hyponatremia and its probable cause in every hospitalized patient, as not every hyponatremic patient needs replacement of sodium. Evaluation should take into account volume status of the patient and urinary sodium content.

Hypovolemic hyponatremia and urine sodium more than 20 may suggest cerebral salt wasting syndrome that needs sodium replacement while normovolemic hyponatremia and urinary sodium more than 20 may denote SIADH (syndrome of inadequate antidiuretic hormone) that is managed by restriction of fluids. Hyperglycemia and hyperlipidemia may result in pseudohyponatremia. Hypervolemic hyponatremia with urinary sodium more than 20 indicates renal failure.

OTHER SPECIAL SITUATIONS

Acute renal failure demands stringent balance between intake and output of fluids to maintain optimum fluid and electrolyte balance. In acute liver cell failure, constriction of the IV volume along with coexistent edema may justify the simultaneous use of IV fluids and diuretics. In acute bronchiolitis, restriction of fluids due to fear of worsening the pulmonary edema is no longer justified, as multiple variable factors are known to increase the fluid requirements in such cases. The same principle holds true in patients with acute brain cell edema where better monitoring in individual patients should decide the actual fluid requirements, rather than routinely restricting fluids to two-thirds the normal maintenance levels. A case of burns is a special situation needing large amounts of fluid replacement, including colloids.

Significant electrolyte disturbances often accompany states or dehydration as well as edema. Clinical judgment of dyselectrolytemia is usually difficult and must be supplemented by biochemical and biophysical monitoring. Serum levels of sodium and potassium should be considered in conjunction with the acid-base status, total body electrolyte content, urinary electrolyte concentrations, electrocardiographic and neuropsychological states. As water and electrolytes are in dynamic equilibrium, correction of one element may precipitate changes in the other, and demands careful handling. Swings from undercorrection to overcorrection are difficult to assess and harmful to the patient. Daily biochemical monitoring is the only guide in optimum management, especially in complex situations.

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CHAPTER 84

Nutritional Support in the Pediatric Intensive Care Unit

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Nutritional failure is a serious problem, especially in patients suffering from subacute or chronic illnesses and also in acute conditions in the younger age group.[1-4] Newborns or young infants may suffer from significant nutritional depletion within 4–7 days of lack of feeding, and ideally need nutritional support to avoid deleterious effects.[5] Nutritional failure may lead to delayed recovery from infection, and wound healing is slow due to impaired immune mechanisms. Prolonged nutritional depletion results in malnutrition with decrease in muscle mass and easy fatigability. This may interfere with normal respiratory effort and cause difficulty in weaning the patient off the ventilator. In addition to a lack of nutritional intake, critically ill children also have increased caloric needs due to catabolic stress. Thus, the goal of nutritional support is to achieve a positive nitrogen balance. This is done by giving 100–120 calories/day and 2–3 g/kg per day of proteins.

The enteral route is always preferred because of ease of administration. It helps to maintain the normal physiological processes of digestion and absorption as it stimulates the gut hormones and enzymes. Also it is safe, cheap, effective and does not need any monitoring. Milk enriched with oil (preferably coconut oil), egg-flips or commercial formulae may be administered through the nasogastric tube, or other semisolids may be fed with a spoon. Necessary supplements of vitamins and minerals as well as extra proteins can be easily supplied through available market preparations.[6]

However, when enteral feeding is not possible or contraindicated, one has to resort to parenteral feeding[6] (especially if enteral feeding is not possible for >4–5 days). The main indications for parenteral alimentation include extremely premature babies [very low birth weight (VLBW)], after major surgical procedures, in post-traumatic conditions, burns, severe gastrointestinal disorders, disseminated infections and multiorgan failure. Total parenteral nutrition (TPN) should be administered ideally by infusions through a central vein and should consist of adequate calories optimally derived from carbohydrates, proteins and fats. Minerals and vitamins should always be supplied. About 55–60% of calories must be supplied from carbohydrates, 30–35% from fats and 5–10% from proteins. Peripheral venous access can also be conveniently used, in which case a concentration of not more than 10–12.5% dextrose solution can be given. In such a situation, fats may be infused in slightly higher amounts to make up for the calories. Proteins are supplied in the form of amino acid mixtures, while fats are provided as intralipids containing adequate essential fatty acids. Commercial solutions for parenteral nutrition are freely available, and are administered through a three-way connection so that infusions of amino acids, intralipids and dextrose are administered separately and get combined at the vein entrance. In infants and children, we preferably use a peripheral venous access. Routine protocol consists of dextrose infusions for the first 3–4 days, followed by additional amino acid mixtures over the next 3–4 days; intralipids are added at a later stage if enteral feeding is still not possible.

Catheter-related complications are rare when a peripheral vein is used. However, infection and sepsis are the most commonly encountered problems. Other complications include hepatic dysfunction and cholestasis, metabolic acidosis, disturbed glucose metabolism, hyperammonemia and fat overload. Vitamin and mineral deficiencies are easily prevented by proper supplementation. Repeated biochemical monitoring is mandatory, and includes daily serum electrolyte estimations, blood glucose, acid-base status, urine examination, frequent liver function tests and other relevant hematological parameters.

Clinical experience with TPN has shown that when used in selected situations, it has improved survival rates in pediatric ICU patients. However, TPN is costly, technically difficult and needs careful monitoring. The cost-risk-benefit ratio should always be considered before starting on this form of nutritional support.

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CHAPTER 85

Pediatric Life-threatening Infections Requiring Critical Care

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GENERAL CONSIDERATIONS

Infections are common in an intensive care unit (ICU) setting. It has been observed that 30–40% of pediatric admissions to the ICU are related to community-acquired infections. A number of other admissions in the pediatric age group are likely to develop infections due to a variety of adverse background factors, e.g. specific organ dysfunction, trauma or surgery. Infections pose a constant threat to life, despite proper treatment with antimicrobial drugs. Prevention, early diagnosis and prompt treatment of existing infections are important challenges faced in the management of pediatric ICU patients.[1-2]

Several factors contribute to the increased vulnerability to life-threatening infections in the ICU. Younger age itself makes a pediatric patient more susceptible to serious infections, as newborns and infants are physiologically more deficient in natural defense mechanisms. Malnutrition,[3] especially when induced by lactation failure, promotes easy access to infection, with quick dissemination of infection, with an increased morbidity and mortality. Developmental defects and anatomical malformations are additional risk factors. Immune deficiency disorders, either congenital or acquired (as in malignancy or in patients on steroid therapy), are also occasionally responsible for infection in the pediatric age group. Children with ventriculoperitoneal shunts or prosthetic valves, and patients with severe burns, are particularly vulnerable to serious infections. Nosocomial infections are difficult to prevent in an ICU setting, especially in patients on ventilators with central lines and other invasive interventions.

The site of infection and host responses to various types of microbial invasions decide the outcome of infections. Intracranial infections, like encephalitis and meningitis, fulminant pneumonias, endomyocarditis and necrotizing enterocolitis may lead to specific organ failure, endangering life. On the other hand, any infection may induce severe immune-mediated responses in the host and may threaten life, as is seen in septic shock, staphylococcal or streptococcal toxic shock syndrome (TSS) and staphylococcal scalded skin syndrome (SSSS).

ETIOLOGY

A majority of serious infections are bacterial, both Gram-positive and Gram-negative. Staphylococcal infections and infections due to *Pseudomonas aeruginosa*, klebsiella and proteus can often turn fulminant and life-threatening. Many other infections in the pediatric age group may require critical care, particularly in vulnerable situations. Tuberculous meningoencephalitis and miliary tuberculosis pose a significant threat to life, especially in infants. It is feared that tuberculosis in human immunodeficiency virus (HIV) infected individuals will constitute a significant proportion of life-threatening infections in the near future.

Viruses also cause life-threatening infections, though not as commonly as bacterial infections. It is difficult to prove viral infections due to constraints of relevant laboratory facilities, though in clinical practice, some of the viral infections can be diagnosed by characteristic clinical findings. These include measles, poliomyelitis and infections due to the herpes virus. Measles encephalitis or pneumonia, poliomyelitis affecting the brainstem or causing weakness of the respiratory muscles, herpes encephalitis and viral myocarditis constitute life-threatening infections in children. Dengue fever and

Japanese B viral encephalitis deserve special mention, as they occur in some parts of our country, and are associated with a significant morbidity and mortality.

Parasitic infections are rarely life-threatening though with a resurgence of malaria, cerebral malaria due to *Plasmodium falciparum* infections is a distinct threat to life. Fungal sepsis is being recognized in patients treated with prolonged antibiotic therapy. In immunocompromized patients, other opportunistic infections such as those due to *Pneumocystis carinii*, toxoplasma and cytomegalovirus may endanger life. Anaerobic bacterial infections may cause serious diseases in certain situations.

CLINICAL APPROACH

It is the high index of suspicion based on clinical experience, evaluation of host factors and knowledge of epidemiology that may lead to an early diagnosis. Newborns and infants may demonstrate a wide spectrum of clinical presentations, some often vague without localization. Refusal of feeds, lethargy, temperature instability, behavior disturbances, disproportionate tachypnea and tachycardia, widened core skin temperature difference, mottling of skin, prolonged capillary refill are some of the symptoms and signs suggesting serious infections. Localizing symptoms and signs of meningitis or pneumonia offer easy clues to the diagnosis and demand close monitoring of specific organ functions.

INVESTIGATIONS

Nonspecific tests like the blood count, acute phase reactants like the erythrocyte sedimentation rate and C-reactive protein, routine urine analysis, spinal tap, chest X-ray may support a diagnosis of infections. Though any acute infection may present with neutrophilic leukocytosis with a shift to the left and eosinopenia, newborns often react with leukopenia. In fact, a normal blood count does not rule out the possibility of infection. Anemia and thrombocytopenia may favor a diagnosis of malaria. Low platelet counts may suggest disseminated intravascular coagulopathy, which may be confirmed by raised levels of fibrin degradation products, and a decrease in coagulation factors. Abnormal cerebrospinal fluid (CSF) may denote intracranial infection, though at times, in children, it is difficult to differentiate partially treated bacterial meningitis from tuberculous meningitis.

Specific diagnosis rests on demonstration of organisms on smear, or culture of blood, CSF, urine, stools or any other body fluids. Pretreatment with antibiotics, and poor techniques including a risk of contamination make the diagnosis of bacterial infection difficult. Often, the clinician has to resort to a presumptive diagnosis of infection based on circumstantial evidence. Special techniques are required to culture viruses and other organisms. Detection of antigen by rapid immunological methods, as well as demonstration of antibodies, is a suitable alternative, though often not easily available. Interpretation of antibody levels against specific infections needs to be considered against the background of local epidemiology. Other tests are required to monitor specific organ functions, and include various noninvasive or invasive interventions.

MANAGEMENT

Specific treatment with chemotherapeutic agents or antibiotics whenever available forms the mainstay of curative management. Obviously, the choice of such a therapy depends upon a precise diagnosis of the infection. As this is often not feasible, empirical treatment is started based on clinical judgment of specific situations. For example, newborns and young infants are covered with a broad-spectrum combination of penicillin and an aminoglycoside (ampicillin + gentamicin). Nosocomial infections may often need newer antibiotics so as to take care of resistant strains of Staphylococci, Pseudomonas and other organisms. Immunocompromized hosts may justify antifungal, antiviral or antiparasitic drugs in addition to antibacterial agents.

Supportive management includes maintenance of fluid, electrolyte and acid-base balance, adequate ventilation and oxygenation, maintenance of optimum cardiac output and circulatory state, and homeostasis of other organ functions. In addition, newborns and sick children need an isothermal environment, especially in centrally air-conditioned units, where special heating devices like radiant warmers are necessary. In special circumstances, even intravenous infusions and humidified oxygen may have to be warmed, as in newborns cold injury is often lethal. Adequate nutrition and a positive nitrogen balance are desirable, and are important, particularly in the long-term management of such patients. Though enteral feeding is the first choice, in conditions where enteral feeds are contraindicated or not tolerated, one may have to resort to total or partial parenteral nutrition.

Having realized that outcome of infection is decided by immunological response of the host, induced by interactions with the organism, immune response modifiers have been tried. These include steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), interferons, growth factors, intravenous immunoglobulins, monoclonal antibodies and naloxone. Transfusion of blood and its components, as well as exchange transfusions have also been tried. All these measures have given equivocal results and many of them are costly, rarely available in developing countries, and may produce considerable side effects. With the exceptions of a few agents, most of them cannot be advocated for routine use.

PREVENTION

Early diagnosis and prompt treatment of trivial infections often prevent life-threatening infections. Vaccine-preventable diseases are easily controlled by proper immunization. Hand washing, proper asepsis and use of disposables go a long way in preventing nosocomial infections. ICUs should formulate specific policies regarding entry of staff and visitors, isolation of patients, disposal of patients' excreta and infected secretions, general cleanliness, fumigation, sterilization of

equipments, bacteriological surveillance and antibiotic usage. All such infection control measures should be monitored by specially designated staff guided by an infection control committee, comprising of clinical and laboratory experts. Prophylactic antibiotics are best avoided in general, as they may often lead to infections by resistant strains of organisms. In certain situations, postoperative antibiotic prophylaxis may be used for one or two doses.

SPECIAL INFECTIONS

Viral Infections

Most viral infections are self-limiting, though at times they may result in serious complications. It is not always possible to anticipate complications but early diagnosis of complications is mandatory to save life. Viral infections may present with biphasic fever and normally the second phase is shorter with lower degree of fever. However, if the second phase presents with drowsiness and oliguria, it suggests a capillary leak and demands urgent intravascular resuscitation. Similarly, development of new symptoms such as severe abdominal pain or vomiting may herald onset of complications.

Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are characterized by evidence of plasma leakage in terms of hemoconcentration (>20% rise above base level or area-specific cut-off around 36%) with the ultrasonography (USG) showing pleural effusion, ascites and gallbladder edema, hepatomegaly, splenomegaly and perinephric fluid. USG findings are sensitive in diagnosis of DHF and DSS. Hepatitis and macrophage activation syndrome (MAS) are the known complications of viral infection.

Influenza viral infection resulted in the recent pandemic due to H1N1 virus. In India, the recent epidemic affected more young people than old with significant mortality in hospitalized patients. Severe disease was seen in children aged 5–12 years. High-risk situations include malnourished children and those with congenital malformations such as heart defects. Acute respiratory distress syndrome (ARDS) is a common complication of influenza; tachypnea in a child suffering from influenza-like syndrome justifies treatment with oseltamivir pending proof of diagnosis by throat or nasal swab.[4] Besides anti-viral drug therapy, such a child would obviously need proper management of respiratory failure.

Central Nervous System Infections

Meningococcemia with or without meningitis is a life-threatening disease. Acute onset of fever followed by purpuric spots offers a clue to the probable etiology. Meningococcemia without meningitis carries a poor prognosis, death resulting from adrenal failure and shock. Development of meningitis denotes ability to localize the disease, and has a better prognosis. Early diagnosis and prompt treatment with penicillin is mandatory for survival.

Other bacteria causing meningitis have many features in common. Risk factors include younger age, marked change in sensorium, focal neurological abnormalities, persistent increase in intracranial tension and gross CSF abnormalities. Besides proper antibiotic therapy (Table 1), control of

Table 1: Empiric antibiotic therapy in pediatric life-threatening infections

Age	*Suspected organism*	*Antibiotic*	*IV dose* (mg/kg/day)
Birth to 3 months (Bacterial Infections)	Gram-positive—Staphylococci— • Streptococci • Listeria	Ampicillin + Gentamicin	200 7.5
		or	
	Gram-negative—*E. coli* • Klebsiella • Pseudomonas	Ampicillin + Ceftazidime	200 200
3 months to 5 years (bacterial infections)	Gram-positive—Staphylococci— • Streptococci Gram-negative—*H. influenzae* • Klebsiella • Pseudomonas	Ampicillin and/or Chloramphenicol Ceftazidime	200 100 200
>5 years (bacterial infections)	Gram-positive—Staphylococci— • *Strep. pneumoniae* Gram-negative—*H. influenza*— • Meningococci	Ampicillin and/or Chloramphenicol + Ceftriaxone	200 100 200
All ages (other organisms)	Herpes virus *P. falciparum* Fungal infections	Acyclovir Quinine Fluconazole	25 25 5

Comments: Therapy is later modified as per bacteriological reports. Other antibiotics which can be used are amikacin 15 mg/kg/day, and vancomycin 30 mg/kg/day.
Abbreviation: IV, intravenous.

increased intracranial tension and seizures is important. Early administration of steroids[5] before administration of the first dose of antibiotic has been shown to be beneficial in minimizing the squeal, especially in *Haemophilus influenzae* and pneumococcal meningitis. Cerebral edema in tuberculous meningitis requires prompt control with mannitol (2 g/kg per day in 4–6 divided doses), and steroids (hydrocortisone 10 mg/kg per day). Hydrocephalus should be treated by a timely ventriculoperitoneal shunt. Ideally, patients suffering from meningitis should undergo continuous monitoring of intracranial pressure; this however is not possible in most of the institutions in our country.

Cerebral malaria is an immune-mediated disseminated vasculitis occurring as a result of *P. falciparum* infection. Diagnosis is difficult unless blood smears demonstrate parasites. In many situations, clinical suspicion may justify therapy with quinine (25 mg/kg per day). Mortality is high unless promptly treated early in the course of the disease.

Herpes encephalitis may be considered in the presence of xanthochromic CSF and localized temporal lesions, as evidenced by an electroencephalography (EEG) or a computed tomography (CT) scan. Early institution of therapy with acyclovir (25 mg/kg per day) is life-saving.

Toxic Shock Syndrome[6]

Though most of the superficial infections of skin and soft tissue are benign, a few toxin-producing strains of Staphylococci and Streptococci may lead to a fulminant infection with the development of shock. Such infections often follow trauma or surgical procedures. If not recognized early, they may be fatal.

Staphylococcal Scalded Skin Syndrome[7]

This syndrome is seen primarily in younger children; at times, epidemics in newborn nurseries have been reported. It is a toxin-mediated disease, characterized by skin lesions which vary from bullous impetigo to widespread exfoliative dermatitis. Early recognition and treatment are mandatory for survival.

Septic Shock[8]

Cardiac output is manipulated in children mainly by altering the heart rate, and not by significant changes in the stroke volume. There is therefore limited ability to maintain cardiac output in adverse situations, often resulting in early decompensation in shock. Thus progression from sepsis to severe sepsis, and thence to septic shock and multiple organ dysfunctions occurs rather rapidly in children. Recognition of early sepsis and of the reversible stage of shock assumes added importance in proper management. Apart from this, the pathogenesis and management of septic shock in children are similar to that in adults.

INFECTIONS IN THE IMMUNOCOMPROMIZED AND CRITICALLY ILL CHILDREN

These differ not only in etiology but also in clinical presentation. Many of these children have serious infections without any fever. Clinical symptoms, signs and progression vary a great deal and aggressive treatment is mandatory in these individuals.

Any infection in newborns and infants must be viewed as a potentially life-threatening one; the distinction between mild or trivial and life-threatening infections however is not easy, and calls for sound clinical judgment.

Table 1 details the empiric treatment of acute fulminant pediatric infections, and lists the important drugs, their dosages and the common organisms encountered in life-threatening pediatric infections.

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CHAPTER 86

Acute Kidney Injury in Infants and Children

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NORMAL RENAL PHYSIOLOGY IN INFANTS AND CHILDREN

Renal function starts to develop in the fetal period and continues to evolve throughout the first years of life until it reaches its complete adult level. The human kidney begins to develop in the 5th gestational week and starts to produce urine between the 10th and 12th week of gestation. Nephrogenesis is complete around the 35th–36th week so that a term neonate is born with all its nephrons, something which is not the case for a premature one, born before nephrogenesis is complete.

The kidney regulates homeostasis by two fundamental functions: (1) the glomerular and (2) the tubular. In neonates, both the functions are deficient and although the neonatal kidneys are well equipped to sustain physiological processes, they are severely limited in their response to stress.

Neonates have glomerular filtration rate (GFR) as low as 20 mL/min/1.73 m^2 at birth, which rises gradually to reach the adult rates at 18 months. Additionally, due to immature tubular function, neonates have reduced concentrating capacity, negative sodium equilibrium and reduced bicarbonate levels and they are, thus, prone to dehydration and hyponatremia.

NORMAL RENAL FUNCTION TESTS IN INFANTS AND CHILDREN

Serum creatinine measured at birth reflects the maternal renal function rather than the infant's renal function. In term babies, the serum creatinine normally rises in the first 24–36 hours after birth, subsequently decreasing and stabilizing at approximately 0.4 mg/dL by 5 days of age.

Table 1: Normal serum creatinine concentrations at different ages

Age	*Serum creatinine (mg/dL)*
Term neonates (<34 weeks GA)—	
<2 weeks old	0.7–1.4
>2 weeks old	0.7–0.9
Term neonates (>34 weeks GA)—	
<2 weeks old	0.4–0.6
>2 weeks old	0.3–0.5
2 weeks to 5 year	0.2–0.5
5–10 years	0.3–1.0
>10 years	0.6–1.4

In preterm infants, the peak value is at 2–3 days after birth and stabilization occurs after 6 days of age (Table 1).

ACUTE KIDNEY INJURY

Definition

The term acute renal failure has been replaced by the term "acute kidney injury" (AKI) due to many fallacies in the term "acute renal failure". The inability of serum creatinine to accurately reflect kidney function has been especially problematic for clinical research in pediatric AKI. This has resulted in the use of more than 35 definitions of AKI in clinical studies, ranging from small changes in serum creatinine to dialysis requirement. Recognizing a need for a consensus definition of AKI to facilitate clinical research on prevention and treatment of AKI, a consensus definition called the RIFLE classification of AKI based on changes in serum creatinine and urine output was developed by nephrologists and intensive care physicians.

Table 2: Adult RIFLE classification[1]

	Estimated CCl	*Urine output*
Risk	eCCl decreases by 25%	<0.5 mL/kg per hour for 8 hours
Injury	eCCl decreases by 50%	<0.5 mL/kg per hour for 16 hours
Failure	eCCl decreases by 75% or eCCl <35 mL/min/1.73 m^2	<0.3 mL/kg per hour for 24 hours or anuric for 12 hours
Loss	Persistent failure >4 weeks	
End stage	End-stage renal disease (persistent failure >3 months)	

Abbreviations: eCCl, estimated creatinine clearance; pRIFLE, pediatric risk, injury, failure, loss and end-stage renal disease.

Box 1: Common causes of acute kidney injury in infants

- Renal dysgenesis
- Obstructive uropathy
- Renovascular accidents
- Congenital heart disease
- Dehydration
- Sepsis, hypoxia
- Renal vein thrombosis

Box 2: Common causes of acute renal failure in children

- Prerenal causes—
  - Hypovolemia
  - Hypotension
  - Hypoxia
- Renal causes—
  - Glomerulonephritis
  - Hemolytic uremic syndrome
  - Renal vein thrombosis
  - Acute tubular necrosis
  - Acute interstitial nephritis
  - Hereditary nephritis
- Postrenal causes—
  - Obstructive nephropathy
  - Vesicoureteric reflux
  - Calculi

The RIFLE criteria consist of three graded levels of injury (risk, injury and failure) based upon either the magnitude of elevation in serum creatinine or urine output, and two outcome measures (Loss and End-stage renal disease).

pRIFLE is a pediatric modification of the adult RIFLE classification which is given in the Table 2.

Epidemiology of Acute Kidney Injury[2,3]

The epidemiological characteristics of AKI have changed over the past three decades. There has been an increase in the overall incidence of AKI with the changing etiology of AKI in recent years. Incidences of obstetrical, surgical and diarrheal AKI have decreased significantly, whereas those of AKI associated with malaria, sepsis, nephrotoxic drugs and liver disease have increased.

Causes of Acute Kidney Injury

The common causes of AKI in infants and children are given in Boxes 1 and 2 respectively.

Pathogenesis of Acute Kidney Injury

Various causes of AKI ultimately culminate in the cascade leading to AKI. These causes have been shown in Flowchart 1.[4]

Clinical Features

The clinical features are usually related to the precipitating disease. The signs and symptoms related to renal failure are oliguria, edema, hypertension, pallor, nausea, vomiting and lethargy. At a later stage, the patient may present with mental obtundation progressing to coma due to hypertensive encephalopathy or uremia; gastrointestinal bleeding is often observed.

Diagnosis of Acute Kidney Injury

All premature and full-term infants void within the first 24 hours after birth. If an infant does not void in 24 hours, a search should be initiated for underlying abnormalities. In the majority of patients with AKI, the common causes are mainly extrarenal; renal causes are responsible for AKI in only a few patients.

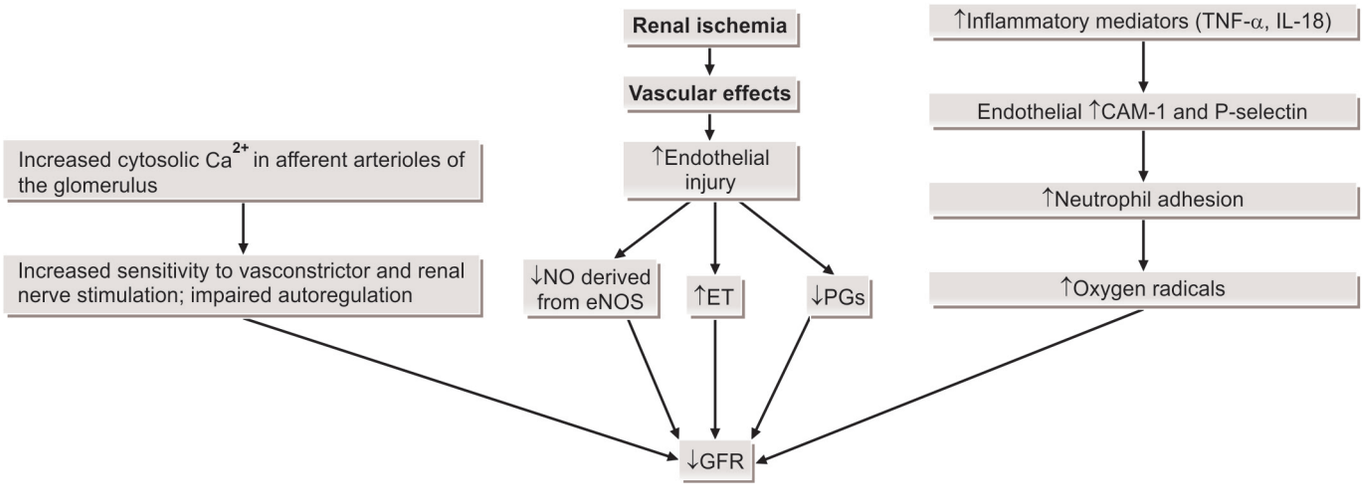
History

A careful history will aid in the diagnosis in a majority of patients. Vomiting, diarrhea and fever suggest dehydration. At times, these symptoms may be present in a patient with hemolytic uremic syndrome (HUS) or renal vein thrombosis. A history of a throat or skin infection will suggest the diagnosis of post-streptococcal glomerulonephritis. History of exposure to drugs (antibiotics, analgesics or other forms of therapy) may suggest interstitial nephritis due to drugs. Presence of a mass in the renal area may suggest diagnosis of renal vein thrombosis or tumor. Presence of rash, purpuric spots, with history of arthralgia or fever may suggest the diagnosis of Henoch-Schonlein purpura or systemic lupus erythematosus (SLE).

Laboratory Investigations

- *Urine examination* is of utmost value in cases of renal injury. Presence of proteinuria and hematuria with red blood cell casts point to a glomerulonephritis, while urine with a large number of pus cells indicates urinary tract infection. The urine may be normal in acute tubular necrosis and in obstructive uropathy.

Flowchart 1: Various causes of AKI



Abbreviations: NO, nitrous oxide; ET, endothelin; PG, prostaglandin; GFR, glomerular filtration rate.

Table 3: Urinary indices which distinguish between prerenal and renal causes of acute renal failure

	Prerenal	*Renal*
Urinary Na (mEq/L)	<10	>50
Fractional excretion of Na (%)	<1	>2
Urine osmolality (mOsm/kg H_2O)	>500	<300
Urine/Plasma osmolality	>1.5	<1.2
BUN/Creatinine	>20	20 or less

- *Urinary indices* are of utmost importance in deciding whether renal injury is prerenal or renal in origin but they are not always accurate (Table 3).
- *Biochemical tests* Patients with AKI may have anemia (mild to moderate) with a raised BUN and serum creatinine. Anemia may be due to hemolysis, bone marrow depression due to lack of erythropoietin or blood loss. Presence of leucopenia may be suggestive of SLE or severe sepsis. Thrombocytopenia may indicate sepsis, HUS or SLE. Hyponatremia (most likely dilutional) and hyperkalemia with acidosis are common in patients with advanced renal failure. Positive ANA and anti-DNA tests with diminished complement levels will be present in cases of SLE. The antistreptolysin O (ASO) titer is raised in cases of post-streptococcal glomerulonephritis.
- *Radiology* Cardiomegaly may be noted on chest X-ray due to overhydration and hypertension. Ultrasonography of the kidneys and bladder is of great help in establishing the etiology in AKI. It is mandatory to do this investigation to rule out any correctable pathology. CT scan or MRI of urinary tract and nuclear imaging may be needed in selected cases. In selected patients, a micturating cystourethrogram may be done to rule out vesicoureteric reflux. Renal biopsy may be necessary in a few cases of non-resolving acute glomerulonephritis [to rule out rapidly proliferative glomerulonephritis (RPGN)]. Renal biopsy should also be considered in a patient with prolonged (>3 weeks) duration of AKI.
- *Role of BIOMARKERS*[5] Accessible markers of AKI can be components of serum or urine or can be imaging studies or any other quantifiable parameter. The urine has yielded the most promising markers for the early detection of AKI and further characterization is anticipated, which will qualify these markers as useful tools for the earlier diagnosis, identification of mechanism of injury, and assessment of site and severity of injury. Hopefully, one or more of these biomarkers, either alone or in combination, will prove to be useful in facilitating early diagnosis, guiding targeted intervention and monitoring disease progression and resolution.

These potential biomarkers are not available commercially in India. The potential biomarkers are—
- N-acetyl-β-glucosaminidase.
- β2-microglobulin.
- α1-microglobulin.
- Retinol-binding protein.
- Cystatin-C.
- Kidney injury molecule-1.
- Neutrophil Gelatinase-associated Lipocalin (NGAL).
- Interleukin-18.

MANAGEMENT OF ACUTE KIDNEY INJURY

The treatment of AKI is as follows—
- Assess the circulatory volume by careful physical examination—dry skin and mucus membranes with associated tachycardia suggest dehydration, while peripheral edema with gallop rhythm, hepatomegaly, bilateral crepitations and hypertension point to fluid overload. In doubtful cases, it may be advisable to insert a central venous catheter for accurate assessment of central venous pressure.

Table 4: Emergency treatment of hyperkalemia

Drugs	*Dose*	*Onset of action*	*Duration of action*
Calcium gluconate	0.5 mL/kg over 5–10 minutes, slowly	Within minutes	30–60 minutes
Sodium bicarbonate	1–2 mEq/kg over 15–30 minutes	Within minutes	1–2 hours
Dextrose with insulin	0.5–1 g/kg dextrose with 0.1–0.2 units insulin/kg slowly	Within minutes	2–4 hours
Kayexalate	1 g/kg in 70% sorbitol orally, or in 30% sorbitol as a retention enema	30 minutes	4–6 hours

- In cases of suspected hypovolemia, give a fluid challenge—10–20 mL/kg of normal saline. Avoid hydroxyethyl starch (voloven) for volume expansion, which has shown to increase the incidence of AKI and the need for dialysis. Normal saline or ringer lactate is an ideal solution for this purpose.
- Avoid use of diuretics and vasopressor agents till hypovolemia is corrected.
- If there is adequate response with fluid challenge continue fluid replacement under close medical supervision.
- If response to fluid challenge is inadequate, as judged by the urine output, do not give more fluids as the patient may have developed acute tubular necrosis. Excess fluid may produce overhydration, hypertension and congestive cardiac failure.
- A trial of diuretics is given after correction of hypovolemia—furosemide 1 mg/kg is given intravenously and the response is noted. If the response is poor, give a higher dose (up to 10 mg/kg), and this may be repeated every 6–8 hours.
- A high dose of furosemide helps in converting oliguric renal failure to nonoliguric renal failure. This helps in clinical management as hyperkalemia and hypervolemia are less likely to occur in patients with nonoliguric renal failure, but it does not alter the underlying condition or prognosis.
- Low dose of dopamine (1–2.5 µg/kg) may help in improving the renal circulation and urine output but use of low dose dopamine is now avoided.
- Hyperkalemia should be promptly corrected as suggested in Table 4.
- *Management of established renal failure* Management of acute tubular necrosis (a common and important pathology) is briefly described below. It aptly illustrates the basic principles of treatment in established acute renal failure. Good conservative therapy will go a long way in preventing complications and avoiding or postponing the need for dialysis. Most of these patients have oliguric renal failure and usually do not respond to volume load and the use of furosemide as described above. These patients should then be treated as follows—
  - Thorough daily physical examination.
  - Maintenance of accurate intake and output charts (record output from all sources) with record of daily weight.
  - Daily laboratory investigations—HB, PCV, BUN, serum creatinine, serum electrolytes, arterial pH and arterial blood gases; chest X-ray for cardiac size and evidence of pulmonary congestion.
  - Intake to be restricted as per output + 400 mL/m^2 per day.
  - Paying particular attention to serum potassium and avoiding fruits, fruit juices, coconut water, dry fruits, chocolates, soups and soft drinks to prevent hyperkalemia.
  - Replace or restrict sodium as needed.
  - Use diuretics in cases of volume overload.
  - Avoid an in-dwelling catheter unless the patient is unconscious, as a catheter is a potential source of infection.
  - Maintain nutrition giving sufficient calories with a high carbohydrate and low protein (0.5–0.7 g/kg) diet; however, proteins should not be unduly restricted to avoid dialysis as this may cause malnutrition, if prolonged.
  - Antibiotics are administered if needed. Avoid nephrotoxic drugs as far as possible. If they have to be used, give in appropriate dosages, preferably monitoring blood levels.
  - Use sodium bicarbonate to counter acidosis.
  - Control hypertension. For severe hypertension, administer diazoxide, hydralazine or a calcium-channel blocker sublingually. In patients with mild to moderate hypertension, use beta-blockers or alpha-methyldopa together with a diuretic.
  - In cases of AKI due to systemic or intrinsic kidney diseases like post-streptococcal glomerulonephritis, Henoch-Schönlein purpura, systemic lupus erythematosus or crescentic glomerulonephritis, in addition to general therapy for AKI, additional therapy like immunosuppressive drugs, corticosteroids, or plasmapheresis with plasma infusion may be required.

Renal Replacement Therapy (RRT)

Even with good conservative therapy some patients will require dialysis. Dialysis may be either peritoneal dialysis (PD), hemodialysis (HD) or continuous arteriovenous hemofiltration (CAVH).

Peritoneal dialysis is safest but cannot be done in patients with recent abdominal surgery, hypercatabolic patients with severe metabolic acidosis or severe volume overload, or in patients with severe respiratory distress. HD requires vascular access and the availability of a dialysis machine with

trained staff. It also requires use of heparin. Even minimal use of heparin cans produces bleeding and hypotension in some patients. Patients with cardiac instability do not tolerate this form of dialysis. Critically ill patients in a catabolic state or even severely overhydrated patients may be treated with CAVH or continuous arteriovenous hemodiafiltration (CAVHD). This form of dialysis is life-saving in critically ill patients and can be done in an ICU setting when it is difficult to transfer the patient to the dialysis unit. However, it requires an expert technical know-how and a good ICU setup. Fluid removal to the extent of 100–300 mL or more per hour may be possible and may require large fluid replacement with close monitoring of patients. It also requires use of heparin in large dosages and may therefore produce bleeding. Patients with prolonged oliguria and those who require hyperalimentation are ideal candidates for CAVH or CAVHD.

- Absolute indications for dialysis are as follows—
  - Gross overhydration.
  - Intractable hyperkalemia.
  - Severe acidosis.
  - Signs and symptoms of uremia.
  - Severe prolonged oliguria during which period hyperalimentation is necessary to maintain an adequate caloric intake.

Renal Replacement Therapy in Neonates

Renal replacement therapy in neonates has a high morbidity and mortality during acute and chronic treatment phase. In general, RRT is only indicated if aggressive symptomatic treatment fails to manage life-threatening conditions such as hyperkalemia, fluid overload, severe acidosis or hypertension. PD or CAVH or continuous venovenous hemofiltration (CVVH) have been done in small series of patients. PD is the method of choice because of its simplicity, easy availability, effectiveness and relative safety in any age group including low birth weight neonates and infants. CAVHD and CVVHD are the treatment of choice in patients with very significant fluid overload and in refractory acidosis as well as severe catabolic renal failure. This mode of therapy requires an expensive machine with a special hemofiltration cartridge as well as tubing for neonates. The risk of hypotension and bleeding is very high. This should be done in very well experienced units only. However, many ethical and medical problems have to be considered in decision-making.

Renal Replacement Therapy in Children

Renal replacement therapy becomes mandatory when conservative treatment fails, and the child develops signs and symptoms of uremia, fluid overload, hyperkalemia, electrolyte imbalance or severe refractory acidosis. Three modalities of therapy are available: (1) PD; (2) HD or (3) continuous arteriovenous or venovenous hemofiltration (CAVH or CVVH) (Box 3).

Box 3: Types of renal replacement therapy

Peritoneal dialysis
It is relatively easy to perform and can be done with the availability of pediatric size PD catheter and PD fluid. It is safe and easily tolerated by most patients including very small patients, and hypovolemia or hypotension is less likely to occur with this procedure compared to HD or CAVHD/CVVHD. However, fluid removal is limited in patients with hypotension, abdominal distension with respiratory embarrassment and a high risk of infection is likely.

Hemodialysis
HD is very effective in treating hyperkalemia, acidosis and fluid overload. HD requires availability of HD machines along with special hemodialysis cartridges and very well trained staff as children tend to develop hypotension.

CAVH/CAVHD
Easy to perform and does not require any special continuous renal replacement therapy (CRRT) machine. The main disadvantages are the need for good arterial access (femoral) and continuous anticoagulation with heparin. It is difficult in patients with hypotension.

CVVH/CVVHD
This is very good for catabolic patients and patients who require removal of large amounts of fluid. However, this modality requires access to a CRRT machine, special hemofiltration cartridge, patient immobilization and anticoagulation.

Recovering Phase of Renal Failure

A patient may remain in the oliguric phase for 3 days to 3 weeks, and at times, even longer. After this, the patient passes into the diuretic phase. In this phase, the patient starts passing large quantities of urine; close monitoring of fluids and electrolytes is mandatory as these patients may get dehydrated and/or have severe electrolyte imbalance. This phase lasts for a few days. The commonest error committed by the physician during the management of this phase is chasing the urine output for a prolonged period. The urine output should be chased (intake increased as per urine output) for the first 2–3 days; subsequently the intake should be gradually decreased over the next 2–3 days. The electrolytes should be carefully monitored, as hyponatremia and hypokalemia are frequently observed.

Long-term Effects of Acute Kidney Injury

Previously it was thought that AKI once recovered has no long-term effects. However, recent studies have shown that AKI is not benign in the long term and may have adverse renal and cardiac consequences. Development of hypertension, chronic

kidney disease, end stage renal disease, atherosclerosis and coronary artery disease have been seen to develop at a later age in the survivors of AKI. Thus, children who have recovered from AKI should be followed up regularly.

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SECTION

24

End of Life Care in the Intensive Care Unit

- End of Life Care in the Intensive Care Unit

CHAPTER 87

End of Life Care in the Intensive Care Unit

"It is not death I fear to face, it is dying."

—Robert Louis Stevenson

INTRODUCTION

Death stalks the intensive care unit (ICU) frequently; it is the final arbiter of life. Pascal, the famous French scientist philosopher, has aptly said, "on mourra seul—one dies alone". I have often wondered what it must feel when one is actually dying. One shall never know until one's time comes. It is the duty of a physician to ease a patient's transition from life to death, from one state of being to another. Even so, some die peacefully and some die after a struggle.

There are a number of problems and challenges an intensive care physician faces with regard to critically ill patients who have reached the end stage of their lives. To start with there is the difficulty in predicting outcomes in individual patients in the early course of their critical illness. Then, there is the difficulty in assessing the patient's wishes and preferences with regard to his or her management, particularly at a point in time when death seems near. The challenges of decision-making, the problems in communication with family and friends in whom emotions run riot, and, last but not the least, the concerns on how best to manage and ease the last days and hours of a patient are both formidable and distressing.

The first question one always needs to ask is—what time frame does one apportion as the end of life? Does one compute the end of life in hours or days or weeks? It is not always easy to answer this question. One can do so, for example in a patient with fulminant sepsis who is pulseless, without a recordable blood pressure, who has failed to respond to all that medical science has to offer. In a patient such as this, the writing is on the wall. On the other hand, take a patient who for some reason is admitted to the ICU, who has widespread metastatic cancer, who refuses chemotherapy or for whom no chemotherapy is possible. This patient too is approaching the end, but it may take weeks or even a few months for him or her to cross the line.

It is perhaps better to consider care of a terminally ill patient rather than end of life care, because it is easier to define a terminal illness rather than the end of life. A terminal illness is one which is deemed incurable and in which death is inevitable and usually imminent. In the ICU, a terminal illness may last for a few hours or at most a few days. It is important in a given patient to review the word terminal from hour to hour or day to day. Occasionally what appears terminal at one point offers hope after a lapse of time. Patients judged terminal by the treating physician have been known to get well and go home. The responsibility of judging a patient as terminal is therefore immense. At times the decision is easy and at times difficult. Clinical judgment, experience, wisdom are all involved in this decision. It may be impossibly difficult to decide when and where to draw the line. If there is indeed the slightest doubt, it is better for all concerned to continue critical care, and review events from time to time. Yet on a number of occasions, the discerning physician can see the nearness and inevitability of death. The resource crunch in health care all over the world (particularly in poor countries) should prompt the physician in such a situation to refrain from using medical technology that merely prolongs death, or that makes death excessively lonely, gruesome, dehumanizing, perhaps even obscene, and ruinous to the patient and the family.

It is important in an acute illness which in spite of all efforts appears to progress relentlessly to an inexorable fatal outcome to ascertain the wishes of the patient and the family. It is equally important never to forget that the patient

comes first and foremost and then the family. The patient in our part of the world invariably follows the physician's advice and the relatives too are similarly influenced. This is indeed an added and extremely heavy responsibility on the physician because poor judgment can unnecessarily prolong the act of dying and can also in the bargain financially cripple the patient's family. Better judgment could have perhaps prevented this calamity. Judgment is terribly difficult, particularly when it concerns young patients in the prime of their lives. Alas! It is not always that a Daniel comes to judgment.

A decision not to initiate invasive support, for example, the use of a ventilator, or the use of dialysis in a terminally ill patient is far more easy than the decision to withdraw support that has already been initiated at a point in time when the life-threatening acute illness seemed potentially reversible. A detailed discussion with the family and close friends plays an important role in decision-making. The family needs to be persuaded to accept that there comes a point in time when intensive care is futile and when support in all forms is either not initiated or withdrawn.

The practice of withdrawing support in all forms when death is close and inevitable varies in different parts of the world. It is an accepted practice in the Western world. It is also increasingly practiced in India, notwithstanding the legal issues involved. Management of terminal illness is further helped by the following principles—

- The physician should under no circumstances administer a drug or perform an act which purposefully kills the patient. There is therefore a distinction drawn between the act of killing and allowing to die.
- Withholding treatment in a terminal illness (end stage of life) is legitimate and an act of compassion. Withdrawal of life support and treatment in the West is considered the equivalent of withholding treatment. The acceptance and practice of withdrawal of support is however contentious and varies in different civilizations.
- The doctrine of "double effect" permits assertive symptomatic treatment with medication for patient relief and comfort, even if this treatment inadvertently causes death—example, the use of morphine with the express purpose to relieve pain or breathlessness can inadvertently lead to death from respiratory arrest.
- Palliative care is not just related to relief of pain, breathlessness and other forms of physical discomfort, but is also concerned with resolving anxiety, restlessness, delirium, irritability and in offering emotional and spiritual support to the patient. It therefore involves care in every aspect of the word.
- The proper training of doctors, nurses and students in the management of terminal illness with special reference to palliative care is of great help.
- The offering of true compassion to patients—a quality that can neither be bought nor taught, but which should come naturally to all well-trained staff in good centers.

COMMUNICATION WITH PATIENTS, FAMILY OR SURROGATES[1-3]

Communication with the family, friends and the patient if he or she is conscious and without cognitive impairment is of vital importance. It is important to discuss at length, without using technical jargon, the nature of a patient's illness, what has been done for the patient, the complications during his or her illness, the measures taken to counter them, the reasons for a deteriorating state and why further measures are not likely to help the patient, but merely prolong the act of dying. It is of immense help if communication with the family is established early, from the time of admission, and continued on a daily basis. The communication should be detailed and take into account the emotional trauma the near and dear ones of a dying patient go through. Here again a note of true compassion and caring goes a long way in making the family understand the overall picture as the physician sees it. In spite of every practiced art of communication, in our country it is at times difficult to convince relatives and friends that the end is near and that further treatment will be of no avail. It is doubly difficult to convince them to allow discontinuation of life support systems. It is wise in our prevailing legal and social circumstances not to withdraw support if the family of a terminally ill patient insists that the support system be continued. Emotions often run riot among relatives of Indian patients under these circumstances, and not respecting these wishes may cause legal problems both for the intensivist and the hospital concerned.

It is equally important to communicate with the patient provided he or she has retained the cognition to allow communication. It is a cardinal principle to keep the patient informed of what is happening to him and as to what measures you as a physician are taking to help him get well. A crucial question that arises is—Does the intensivist tell the patient the truth about his illness—that he or she is dying or will soon die? In the West, particularly in the United Kingdom and the United States of America, the whole truth is told particularly when a specific question with regard to the possibility of impending death is put to the physician. But social and ethical norms are different in the east as also in many countries of Eastern Europe and South America. In my experience, it is very rare for a patient in our country to ask the physician a direct question—Will I die? Am I dying? Will I never get well? In fact, almost always, even a doctor in our part of the world, who is dying and remains conscious and cognitive, will not talk of death. What is more if one does directly or indirectly touch on the subject, the patient invariably changes the conversation. In our social set up, it would be wrong to tell the bitter truth to a dying patient. It is not the calling of a physician to add to a patient's anguish, to extinguish the flickering flame of hope burning in every patient's heart, however close he may be to death. It is however extremely important to tell the truth and nothing but the whole truth to the patient's family and friends.

END OF LIFE DECISION-MAKING[4,5]

Decision-making in relation to end of life patient care should involve the physician, the patient, the family of the patient or the surrogates. The patient and the family have the right to information. Involving family friends and surrogates is vital in the decision-making process, considering that a large number of ICU patients lack the capacity to decide. A large number of factors may influence a physician's attitude and recommendations with regard to end of life questions and decisions. These include his religion, his upbringing, social and ethical norms prevailing in the country he practices in, his philosophy and outlook on life. Whatever these may be, he needs to consider and integrate the patient's and the family's views and values into his recommendation for the holistic care of the dying patient. Also his recommendation must be clinically realistic, beneficent and morally irreproachable. This is easier said than done, more so if the approach of the family and friends is palpably wrong or unrealistic. Here again, it is good communication that holds the key to an integrated decision-making process, communication which starts early, on admission of the patient, and not just when the patient is close to the end of life.

A simplified mnemonic for effective patient family communication is VALUE. *V*alue and appreciate what is said by family members, *A*cknowledge the family member's emotions, *L*isten, *U*nderstand who the patient is as a person, *E*licit questions from family members.[6]

It should be realized that there is no protocol that can be followed in the end of life decision-making process. Nor are there likely to be any sensible evidence-based guidelines on this issue, and obviously no randomized controlled studies to help the physician in this important aspect of life! This is because each human being is a unique individual and the problems and challenges to guide the patient, family or surrogates through the decision-making in the ICU will have special unique aspects.

In spite of kindness, compassion, wisdom and good clinical judgment, the physician may find himself in an irreconcilable conflict—either ethical, moral or clinical with the patient's family or surrogates. Here again frank open and often lengthy communication may be the key to the problem. If problems still persist, the physician should advise mediation through the Ethics Committee of the hospital.

TREATMENT GOALS AT THE END OF LIFE

The answer to the management of an incurable terminal illness in the ICU lies in the practice of palliative care, which includes the practice of palliative medicine. The latter has now become a speciality which deals with various physical and emotional vicissitudes encountered in the terminally ill. Pain control has evolved far beyond the mere administration of opiates, opiate derivatives and sedatives. Yet in poor countries, these drugs still remain the sheet-anchor of pain control. Many doctors, nurses and health care workers fail to use an appropriate dose of opiates or their derivatives for fear of depressing respiration and circulation, thereby endangering life or hastening death. In this connection, a quote from a judgment delivered in the United Kingdom by Judge Delvin is indeed of unsurpassed guidance and relevance—"The proper medical treatment that is administered and that has an incidental effect in determining the exact moment of death is not the cause of death in any sensible use of the term".[5]

The World Health Organization (WHO) defines palliative care as follows—The act of total care of patients whose disease is not responsive to curative treatment. Control of pain or other symptoms and of psychological, social and spiritual problems is paramount. The goal of palliative care is the achievement of the best possible quality of life for the patient and the family.

Palliative medicine is comparatively cheap. It respects life and considers death as a natural inevitable sequel. When correctly practised, it neither protracts the art of dying nor generally hastens it. It helps to support the patient in the transition from life to death and lends support and comfort to those close to the patient during this period of time. Palliative medicine when practised with an equal measure of skill and compassion should hopefully render the current commotion and debate on euthanasia in the West obsolete.

WITHDRAWAL OF LIFE SUPPORT[7,8]

In India, this indeed is both a difficult and thorny problem. It is easy to go off inotropes, vasopressors, intravenous (IV) fluids, dialysis, to remove invasive lines, catheters, etc. Other interventions such as pacemakers, antibiotics and monitors can be stopped once a decision to end life-support has been made. Does one inform the patient before withdrawing life support? In the West, particularly in the United States of America and the United Kingdom, they do so. Ethical, philosophical and social values differ in different civilizations. The practice in India is not to inform a conscious patient on the decision to withdraw support. I well remember a patient who had a suspicion that we were going to withdraw support. He turned to me with a piteous look and said, "Doctor, have you decided to abandon me?" The question of informed withdrawal obliviously does not arise in an obtunded or comatose patient.

There are two further debatable points in relation to withdrawal of support. Should one stop fluids and nutrition? And the next question—should one withdraw ventilator support in a patient who has already been on it? There are many intensivists who would say "Yes" to both these questions when referring to a terminal illness in the ICU. But much can be said on both sides. Does palliative care not look to the comfort of the patient? Parenteral nutrition is of course stopped both because of its futility and expense. Yet does stopping fluids and basic nutritional support, either orally or through a nasogastric tube already in place, disturb significantly the comfort level of a dying patient, particularly if he is awake and conscious? We are told that there is no proof that it does so. But an absence of proof is not a proof of absence. Also, does giving fluid or some oral nutritional

support significantly prolong the act of dying? I for one do not think so.

Removing ventilator support in a comatose patient just about to die is a practice observed in all units in the West and in many units in our country. To do so in a dying patient who is conscious could certainly produce significant discomfort to the patient as also to those around the patient. It should be noted that the law in India prohibits the withdrawal of ventilator support, though many units do practice withdrawal when the end is near.

There are no cut and dry definite answers to many questions relating to life and death. There is no absolute right. There are shades of right and wrong. The shades one opts for depend on one's philosophy of life and death, on social, moral and religious beliefs and on the law of the land one lives in.

In conclusion, the management of a terminal illness lies in caring for the dying patient. Is it perhaps too much to ask that the physician should care for death and dying as much as he cares for life and living?

The lines of John Donne come to mind—

> "Every man's death diminishes me,
> For I am concerned with the whole of mankind.
> Therefore, send not to ask for whom the bell tolls.
> It tolls for thee."

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Appendix

1. Normal Blood Gas and Respiratory Parameters, and Gas Transport Equations

Abbreviation	*Parameters (full form)*	*Equations*	*Normal values*
pH			7.35–7.45
PAO_2	Partial pressure of oxygen in alveolus		104 mm Hg
$PACO_2$	Partial pressure of carbon dioxide in alveolus		40 mm Hg
PaO_2	Partial pressure of oxygen in arterial blood		75–100 mm Hg
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood		35–45 mm Hg
$P\bar{v}O_2$	Partial pressure of oxygen in mixed venous blood		35–45 mm Hg
SaO_2	Arterial oxygen saturation		96–100%
$S\bar{v}O_2$	Mixed venous oxygen saturation		70–80%
RQ	Respiratory quotient	$\dot{V}CO_2/\dot{V}O_2$	0.8
CaO_2	Arterial oxygen content	$(1.39 \times SaO_2\%/100 \times [Hb]) + (0.0031 \times PaO_2)$	18–21 mL/dL
$C\bar{v}O_2$	Mixed venous oxygen content	$(1.39 \times S\bar{v}O_2\%/100 \times [Hb]) + (0.0031 \times P\bar{v}O_2)$	14–15 mL/dL
$C(a\text{-}\bar{v})O_2$	Arteriovenous oxygen difference	$CaO_2 - C\bar{v}O_2$	4–6 mL/dL
CcO_2	Pulmonary capillary oxygen content	$(1.39 \times [Hb]) + (0.0031 \times PAO_2)$	20–23 mL/dL
$\dot{V}O_2$	Oxygen consumption	$C(a\text{-}\bar{v})O_2 \times CO \times 10$	195–285 mL/min
$\dot{D}O_2$	Oxygen delivery	$CaO_2 \times CO \times 10$	950–1150 mL/min
O_2ER	Oxygen extraction ratio	$C(a\text{-}\bar{v})O_2/CaO_2$	0.24–0.28
$(A\text{-}a)DO_2$	Alveolar-arterial oxygen gradient	$PAO_2 - PaO_2$	
	On $FiO_2 = 0.21$		5-25 mm Hg
	On $FiO_2 = 1.0$		25–65 mm Hg
$\dot{Q}_S/\dot{Q}_T$	Shunt fraction	$(CcO_2 - CaO_2)/(CcO_2 - C\bar{v}O_2)$	3–8%
V_D/V_T	Dead space fraction	$[PaCO_2 - P_ECO_2]/PaCO_2$	0.25–0.4

Abbreviations: CO, cardiac output; P_ECO_2, partial pressure of carbon dioxide in expired gas.

2. Arterial Blood Gases (at sea level) while Breathing Room Air at Different Ages

Age (years)	*PaO_2 (mm Hg)*	*$PaCO_2$ (mm Hg)*	*$(A\text{-}a)PO_2$ (mm Hg)*
20	84–95	33–45	4–17
30	85–94	34–45	7–21
40	80–90	34–45	10–24
50	75–90	34–45	14–27
60	75–88	34–47	17–31
70	70–86	34–47	21–34
80	67–80	34–47	25–38

3. Alveolar Oxygen Tension (PAO_2) in Non-acclimatized Subjects Breathing Air at Sea Level and at Varying Altitudes

(Modified from Cotes JE. Lung Function—Assessment and Application in Medicine. Melbourne, London: Blackwell Scientific Publications; 1979. pp. 463.)

Altitude		*Barometric pressure (mm Hg)*	*PAO_2 (mm Hg)*
Meters	Feet		
0 (sea level)	0	760	102
1500	5000	632	82
3000	10,000	523	61
4600	15,000	429	44
6100	20,000	349	35
7600	25,000	282	33

4. Normal Hemodynamic Parameters and Calculations

See Chapter on Cardiac Monitoring in Adults.

5. Daily Requirements of Important Electrolytes in Critically Ill Patients

Electrolytes	*Enteral nutrition*	*Parenteral nutrition*
Sodium	1.3–3.3 g 60–150 mEq	60–150 mEq
Potassium	2–5.5 g 40–80 mEq	40–80 mEq
Chloride	40–100 mEq	40–100 mEq
Magnesium	350 mg 10–20 mEq	10–20 mEq
Phosphorus	800 mg 10–60 mmoL	10–60 mmoL
Calcium	800 mg 5–20 mEq	5–20 mEq

6. Daily Vitamin Requirements in Critically Ill Patients

Vitamins	*Enteral nutrition*	*Parenteral nutrition*
Vitamin A	3300 IU	3300 IU
Vitamin D	400 IU	200 IU
Vitamin E	10–20 IU	10 IU
Vitamin K	-	10 mg/week IM
Vitamin C	50–60 IU	100 IU
Thiamine	1.5 mg	3 mg
Riboflavin	1.8 mg	3.6 mg
Niacin	20 mg	40 mg
Pyridoxine	2 mg	4 mg
Pantothenic acid	7 mg	15 mg
Folic acid	200 µg	400 µg
Vitamin B_{12}	2 µg	5 µg
Biotin	100 µg	60 µg

7. Daily Requirements of Important Trace Elements in Critically Ill Patients

Trace element	*Enteral nutrition*	*Parenteral nutrition*
Zinc	3 mg	2.5–4 mg
Copper	1.5 mg	1–1.5 mg
Iron	-	1–2 mg
Manganese	150–800 µg	200–800 µg
Molybdenum	75–250 µg	100–200 µg
Selenium	40–120 µg	40–120 µg
Chromium	10–15 µg	10–20 µg
Cobalt	1.1 mg	-
Iodine	-	120 µg

8. Composition of Plasma Compared to Some Commonly Used Crystalloid Solutions

Solution	*Na^+ (mEq/L)*	*Cl^- (mEq/L)*	*K^+ (mEq/L)*	*Ca^{++}/Mg^{++} (mEq/L)*	*Buffer*	*pH*	*Osmolality (mOsm/kg)*
Plasma	141	103	4–5	5/2	HCO_3^- (26)	7.4	289
0.9% Saline	154	154	-	-	-	4.5–7	308
Ringer lactate	130	109	4	3/0	Lactate (28)	6–7.5	273
Dextrose-Saline	154	154	-	-	-	3.5–6.5	586

9. Important ICU Drugs with their IV Dosages and Infusion Rates

9A. Dopamine

Preparation: 600 mg in 500 mL 5% dextrose
Concentration: 1200 µg/mL or 20 µg/microdrop

Desired effect	Dose (µg/kg/min)	Weight (kg)						
		40	50	60	70	80	90	100
		Infusion rate (microdrops/min)						
Renal vasodilatation	1	2	2.5	3	3.5	4	4.5	5
(1–5 µg/kg/min)	5	10	12.5	15	17.5	20	22.5	25
Increase in cardiac output	6	12	15.0	18	21.0	24	27.0	30
(6–10 µg/kg/min)	10	20	25.0	30	35.0	40	45.0	50
Vasoconstriction	11	22	27.5	33	38.5	44	49.5	55
(11–20 µg/kg/min)	20	40	50.0	60	70.0	80	90.0	100

9B. Dobutamine

Preparation: 500 mg in 500 mL 5% dextrose
Concentration: 1000 µg/mL or 16.7 µg/microdrop
Usual Dose: 5–15 µg/kg/min

Dose (µg/kg/min)	Weight (kg)						
	40	50	60	70	80	90	100
	Infusion rate (microdrops/min)						
5	12	15	18	21	24	27	30
10	24	30	36	42	48	54	60
15	36	45	54	63	72	81	90
20	48	60	72	84	96	108	120
40	96	120	144	168	192	216	240

9C. Norepinephrine

Preparation: 4 mg in 500 mL saline
Concentration: 8 μg/mL
Administration: Beta dose 1–10 μg/min
Alpha dose >10 μg/min

Dose (μg/min)	*Infusion rate (mL/hr)*
1	7.5
2	15.0
4	30.0
6	45.0
8	60.0
10	75.0
12	90.0
14	105.0
16	120.0
18	135.0
20	150.0

9D. Nitroglycerin

Preparation: 100 mg in 500 mL 5% dextrose
Concentration: 200 μg/mL or 3.33 μg/microdrop
Dose: Venodilator Dose 1–50 μg/min
Usual Dose 1–400 μg/min

Dose (μg/min)	*Infusion rate (microdrops/min)*
5	1.5
10	3.0
25	7.5
50	15.0
100	30.0
150	45.0
200	60.0
250	75.0
300	90.0
350	105.0
400	120.0

9E. Lidocaine and Procainamide

Preparation: 1g in 250 mL 5% dextrose
Concentration: 4 mg/mL
Usual Dose: 1–4 mg/min

Dose (mg/min)	*Infusion rate (mL/hr)*
1	15
2	30
3	45
4	60

9F. Nitroprusside

Preparation: 50 mg in 500 mL 5% dextrose
Concentration: 100 μg/mL or 1.67 μg/microdrop
Usual dose: In heart failure 0.5–2 μg/kg/min*
In hypertension 2–5 μg/kg/min

Dose (μg/kg/min)	*Weight (kg)*						
	40	50	60	70	80	90	100
	Infusion rate (microdrops/min)						
0.5	12	15	18	21	24	27	30
1.0	24	30	36	42	48	54	60
1.5	36	45	54	63	72	81	90
2.0	48	60	72	84	96	108	120
2.5	60	75	90	105	120	135	150
3.0	72	90	108	126	144	162	180
3.5	84	105	126	147	168	189	210
4.0	96	120	144	168	192	216	240
4.5	108	135	162	189	216	243	270
5.0	120	150	180	210	240	270	300

*In patients with heart failure, 50 mg of nitroprusside are added to 250 mL of 5% dextrose, and the infusion rate is halved.

10. Serum Levels of Commonly Used ICU Drugs

Drug	*Serum levels*	
	Therapeutic range	Toxic range
Paracetamol	10–30 μg/mL	>200 4 hrs post-ingestion
Amikacin	Peak: 25–35 μg/mL Trough: 1–4 μg/mL	>35 >10
Gentamicin	Peak: 5–10 μg/mL Trough: 1–2 μg/mL	>10 >2
Vancomycin	Peak: 40–50 μg/mL Trough: 5–15 μg/mL	>80 >20
Tobramycin	Peak: 8–10 μg/mL Trough: 1–2 μg/mL	>10 >2
Barbiturates – Short-acting – Intermediate acting – Phenobarbitone	 1–2 μg/mL 1–5 μg/mL 15–40 μg/mL	 >5 >10 >40-nystagmus; >65-coma
Lithium	0.6–1.2 mEq/L	>2
Amitryptyline	120–250 ng/mL	>500
Desimipramine	75–160 ng/mL	>1000
Imipramine	125–250 ng/mL	>500
Chlorpromazine	50–300 ng/mL	>750
Diazepam	100–1000 ng/mL	>5000
Pentazocine	0.1–1 mg/L	>2
Pethidine	600–650 μg/L	>10 mg/L
Phenytoin	10–20 μg/mL	>20-nystagmus; >40-mental status
Disopyramide	3–7 μg/mL	>7
Lidocaine	1.5–6 μg/mL	>6
Quinidine	2–5 μg/mL	>6
Procainamide	4–10 μg/mL	>10
Theophylline	10–20 μg/mL	>20
Digoxin	0.8–2 ng/mL	>2
Acetylsalicylic acid	100–350 mg/L	>350

11. Important Drug Interactions in the ICU

(From The ICU Book, 1991. [Ed. Marino PL] Lea and Febiger, Philadelphia, London)

	Serum level	
IV Drug	Increased by	Decreased by
Catecholamines	Agents which alkalinize the urine—diamox	Agents which acidify the urine—Vitamin C
Lidocaine	Cimetidine, beta-blockers	-
Procainamide	H_2-antagonists—cimetidine, ranitidine	-
Beta-blockers – Metoprolol – Propranolol	 Cimetidine Cimetidine, furosemide	 Rifampicin
Aminophylline	Cimetidine, propranolol, erythromycin	Phenobarbital, rifampicin
Digoxin	Quinidine, amiodarone, verapamil, diazepam, erythromycin, spironolactone	Rifampicin
Diazepam	Propranolol	Phenytoin
Phenytoin	Cimetidine	Phenobarbital, rifampicin, diazepam
Pancuronium	Verapamil, clindamycin	Theophylline
Cimetidine		Rifampicin, phenobarbital

12. Compatibility Chart for Commonly Used Critical Care Drugs

From Guglielmo J. Pharmacotherapy. In: Bongard FS, Sue DY (Eds). Current Critical Care Diagnosis and Treatment. New York: McGraw Hill Companies; 1994. pp. 191-8.

Key: C-documented compatibility; M-mixed results; I-documented incompatibility; N-no documented information.

	Aminophylline	Amiodarone	Amrinone	Bretylium	Dobutamine	Dopamine	Heparin	Isoproterenol	Lidocaine	Norepinephrine	Nitroglycerin	Nitroprusside	Phenylephrine	Procainamide	Verapamil
Aminophylline		I	N	C	I	N	I	I	I	C	C	N	N	N	I
Amiodarone	I		N	C	C	C	N	C	C	C	C	N	C	C	C
Amrinone	N	N		N	N	N	N	N	N	N	N	N	N	N	N
Bretylium	C	C	N		C	C	N	N	NC	C	C	N	N	M[1]	C
Dobutamine	I	C	N	C		C	I	C	C	C	C	N	C	C	C
Dopamine	N	C	N	C	C		C	N	N	C	C	N	N	N	C
Heparin	I	N	N	N	I	C		C	I	C	N	N	N	N	C
Isoproterenol	I	C	N	N	C	N	C		N	I	N	N	N	N	C
Lidocaine	C	C	N	C	C	C	C	I		I	C	N	C	C	C
Norepinephrine	I	C	N	N	C	N	I	N	I		N	N	N	N	C
Nitroglycerin	C	C	N	C	C	C	N	N	N	C		N	N	N	C
Nitroprusside	N	N	N	N	N	N	N	N	N	N	N		N	N	N
Phenylephrine	N	C	N	N	C	N	N	N	N	C	N	N		N	N
Procainamide	N	C	N	M[1]	C	N	N	N	N	C	N	N	N		C
Verapamil	I	C	N	C	C	C	C	C	C	C	C	N	N	C	

[1]May be concentration dependent.

Note:

(a) Administration should be done through y-sets. Most compatibilities are visual, i.e. no visible precipitation.

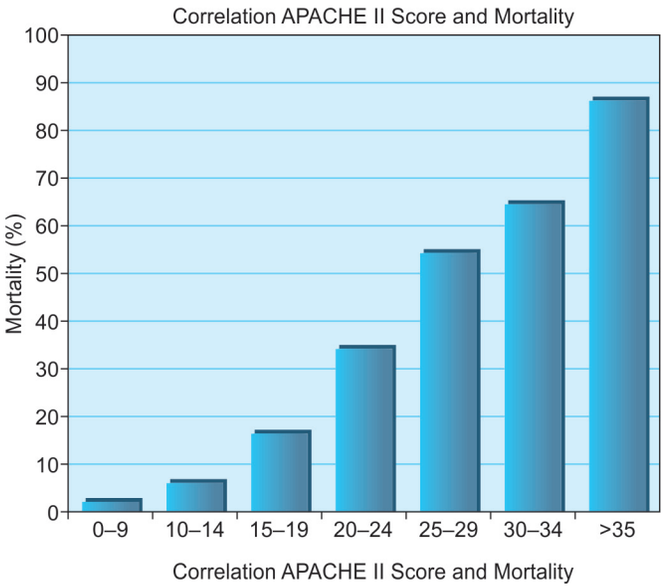
(b) All compatibility data are for 24 hours in D_5W or normal saline. Some combinations may be compatible for shorter durations or under specific conditions.

13. Glasgow Coma Score, Trauma Score, Revised Trauma Score, CRAMS Scale and APACHE II Score

See Chapter on Critical Care Scoring.

14. Correlation between APACHE II Score and Mortality

(From: Breach Candy Hospital ICU data 2001-2003).



15. Criteria for Diagnosis of Brain Death*

[From: ICU Book, 1991, (Ed. Marin PL). Lea and Febiger, Philadelphia, London]

Brain death has occurred if the following criteria are met on two consecutive occasions, at least two hours apart—

1. Does not localize in response to noxious stimuli (i)
2. Body temperature >34°C
3. Serum levels of the following are negligible or subtherapeutic—
   (a) Ethanol; (b) CNS depressant drugs
4. The following movements are absent—
   (a) Decorticate posturing; (b) Decerebrate posturing; (c) Shivering; (d) Spontaneous movements
5. The following reflexes are bilaterally absent (ii)
   (a) Pupillary light reflex; (b) Corneal reflex; (c) Oculovestibular reflex; (d) Oculocephalic reflex (doll's eyes)
6. EEG is isoelectric at maximal gain (iii)
7. Apnea test is confirmatory (iv)
   (a) PaO_2 at end of test_____; (b) $PaCO_2$ at end of test_____

(i) Painful stimuli should be localized to cranial nerve areas because of the risk for spinal cord reflexes with peripheral stimuli. The favored test is supraorbital pressure.

(ii) Pupillary light reflexes can also be absent after eye injury, neuromuscular blocking agents, atropine, mydriatics, scopolamine and opiates.

(iii) Isoelectric EEG does not exclude brainstem activity, and is not to be used in isolation to diagnose brain death.

(iv) The apnea test is confirmatory if there is no evidence of spontaneous ventilatory efforts for at least 3 minutes, and the $PaCO_2$ is >60 mm Hg at the end of the test. If history of chronic CO_2 retention is present, the PaO_2 should be <55 mm Hg at the end of the test.

*Modified from the University of Pittsburgh criteria for brain death, with permission of BC Decker Inc., Philadelphia.

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